Multifactorial aspects of fracture risk in primary care

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Multifactorial aspects of fracture risk in Primary care

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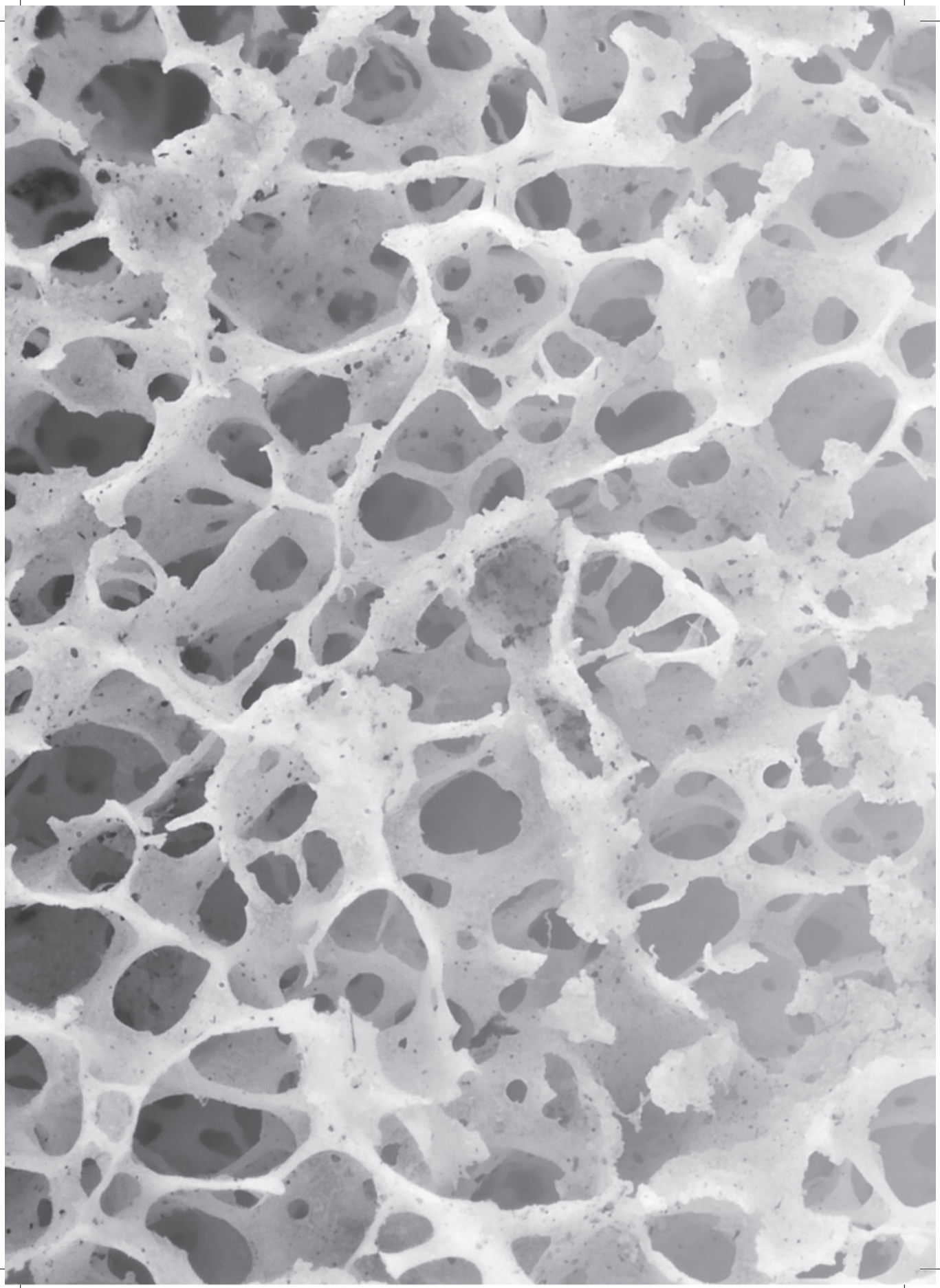

Chapter 1

General introduction and outline of the thesis

1. INTRODUCTION

As people age, bone mass declines, which predisposes to an increased risk of fractures. The decline of bone mass and disruption of bone micro-architecture result in a systemic condition called osteoporosis[1]. With rising life expectancy and the baby boomers starting to reach the age of 65, elderly represent the fastest growing population category in the world, causing osteoporosis to be a major public health problem throughout the world. In the Netherlands, in 2009, the amount of subjects aged 65 years and older was 15% which is expected to rise to 26% during the next 30 years[2]. The number of Dutch women aged 55 years and older with osteoporosis, according to the definition of the World Health Organization, is expected to rise from 640.000 in 2005 to 880.000 in 2025, which would represent an increase of 37% (figure 1)[3]. During the same period, the increase of osteoporosis in men would be over 50%.

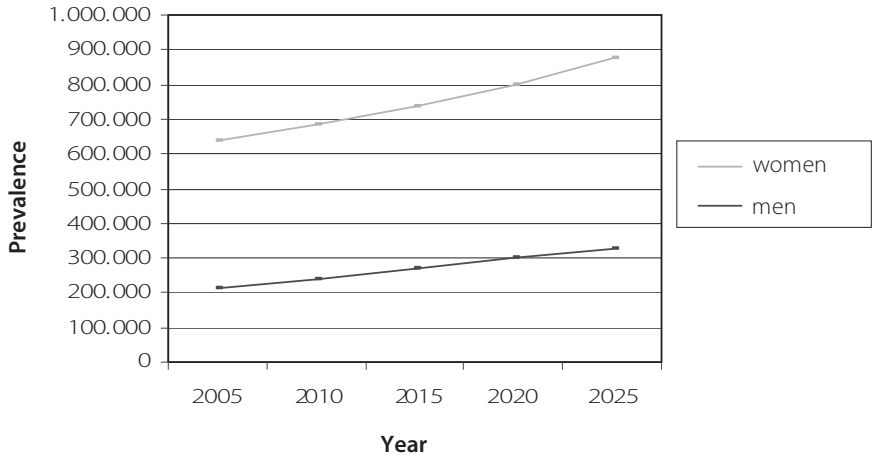

Figure 1 *Expected prevalence of osteoporosis in the Netherlands from 55 years by sex in the period 2005-2025*[3].

2. DEFINITION OF OSTEOPOROSIS

Historically, the term osteoporosis appeared for the first time in medical terminology in France and Germany in the nineteenth century used as a descriptive term emphasizing the porosity of the histological appearance of aged human bone[4]. Nevertheless, prior to the use of the term osteoporosis, an English surgeon named Astley Cooper suggested in his book "A Treatise on Dislocations and Fractures of the Joints" that certain types of fracture may occur due to age-related reduction in bone mass or quality[5]. Age related bone loss starts around midlife and is more prominent in women compared to men[6,7]. It occurs as a result of increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts[7]. In women, an acceleration of the rate of bone loss during the menopause is present, which explains why women are far more likely to develop osteoporosis[7,8]. Osteoporosis is known as a silent disease as most people are not aware of the presence of the condition until they suffer a clinically evident low-energy fracture (fractures resulting from a fall from standing height or lower). In other

cases, osteoporosis may present as backache, height loss or spinal deformity[1]. In 1994 the World Health Organization proposed diagnostic criteria for osteoporosis based on bone mineral density (BMD), which are now widely recognised[9]. This classification system uses T-scores to determine disease severity. A T-score describes the number of standard deviations (SD) that the BMD (expressed in grams of mineral per square centimetre) lies below or above the normal mean value for healthy young adults. According to this classification, osteoporosis is defined as a T-score of ≤ -2.5 SD in the spine and/or femoral neck and/or total hip. A T-score between < -1.0 and > -2.5 SD meets the criteria for osteopenia (low bone mass) and a normal BMD lies ≥ -1.0 SD. When osteoporosis is not caused by some other specific disorder, this is called primary osteoporosis[10]. When a low-energy fracture is present in a subject with osteoporosis, the diagnosis established (severe) osteoporosis is made. Disorders like vitamin D deficiency, renal disease, celiac disease and hyperparathyroidism or use of certain medication can cause accelerated bone loss, as such acting as a contributor to osteoporosis. In this case, it is defined as secondary osteoporosis[11,12].

3. CLINICAL SIGNIFICANCE OF FRACTURES

Fractures can have significant adverse outcomes which fall into three broad categories: mortality, morbidity and costs.

3.1 Mortality

Although increased mortality after hip fracture is best known, it has been shown that all major osteoporotic fractures are associated with an increased risk of mortality[13]. Mortality rates are highest immediately after the fracture and increases with increasing age[13-15]. During a period of five year follow-up, the occurrence of a hip or vertebral fracture showed a strong association with death[16]. Moreover, women with a vertebral fracture had an increased risk of death that rose with an increasing number of vertebral fractures[17] and within the first year after a hip fracture, 10-20% more women died than expected for age[15]. Most of deaths after fracture are not caused by the fracture itself, but by the interaction between co-morbid chronic diseases and the fracture[15]. It has been shown that the risk of death after surgical repair of a hip fracture can be reduced by 28% through pharmacological intervention of low BMD[18].

3.2 Morbidity

Morbidity can be defined as the loss of utilities. Overall, after fracture, a 50 year old white women living in the US has a 13% chance of experiencing functional decline[19]. Osteoporosis related fractures are estimated to cause 6.7% of the women aged 50 years and older to become dependent in basic activities of daily living, and 7.8% are expected to require nursing home care for an average of 7.6 years[20]. In a Dutch sample of independently living elderly, it was shown that during 12 months after injury, patients with injuries to the extremities (80% fractures) did not regain their pre-injury levels of functioning[21]. Recovery was worse in women compared to men[21]. In the same group of patients, it was shown that hip fractures and fractures of the wrist seriously threatened the chance of remaining independent[22]. With

respect to vertebral fractures, utility was lower among persons with prevalent and incident vertebral fractures[23]. It was suggested that the incidence of a vertebral fracture can be predicted by a worse state of health[23].

3.3 Economic costs

In the Netherlands, costs due to osteoporosis related fractures are estimated at €210 million each year. Hip fractures represent the majority of these costs, with on average €25.000 medical costs during the first year after fracture[24]. In the USA, fracture costs are as much as $20 billion each year, with over a third of this total accounted for by hip fractures[25]. Twelve month medical costs following a hip fracture were estimated at more than $30.000 on average, vertebral fractures ranged from $18.000-$23.000 in the year post-fracture, followed by non-vertebral fractures with costs ranging from $13.000 to $14.000[26].

4. PATHOPHYSIOLOGY AND RISK FACTORS OF FRACTURES

The clinical relevance of osteoporosis lies in the resulting osteoporotic fractures. Osteoporotic fractures are the result of a combination of reduced bone strength and increased rate of falls[27]. Many skeletal characteristics contribute to bone strength like shape and geometry (bone macroarchitecture) and the composition of trabecular and cortical bone (bone microarchitecture) as well as the tissue properties. However, in clinical practice, the microarchitectural and tissue properties of bone cannot be assessed properly, and the BMD measurement remains the best available non-invasive indirect assessment of bone strength[27]. Bone mass of an individual in later adult life is a result of the peak bone mass obtained during skeletal growth and the subsequent rate of bone loss[28]. In postmenopausal women, bone loss occurs due to increased bone turnover as a result of oestrogen deficiency and through oestrogen-independent age-related mechanisms[27]. At the cellular level, bone loss occurs because of increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts[7]. With the decline of BMD the risk of osteoporotic fracture increases continuously with a 1.5-fold increase in fracture risk for each standard deviation decrease in BMD[29]. Although the risk of fracture is considerably elevated in subjects with low bone mass, it does not mean that only individuals with osteoporosis will sustain a fracture[4,27]. In fact, the majority of fractures does not occur in subjects with osteoporosis, but in the larger group of subjects with osteopenia[30,31]. Apart from BMD, several other risk factors of fracture have been defined, which should also be taken into account during fracture risk assessment.

4.1 Clinical risk factors for fracture

4.1.1 Falls

Falls are a strong and independent risk factor for low-energy fractures[32-34]. A substantial amount of risk factors for falls in community dwelling elderly has been described. A recent review distinguished a total of 31 risk factors for falls which were assessed by at least five studies[35]. Of these, advanced age and female sex were most frequently studied with an increasing risk associated with both growing age and female sex. Furthermore, several aspects related to disability (*i.e.* physical disability, disability in

instrumental activities of daily life, use of a walking aid) and mobility (*i.e.* reduction in physical activity, muscle weakness, balance impairment, reaction time, and gait) showed to increase the risk of falls[32,35]. An important aspect in fracture risk associated with a fall is the force of impact, in which the way of falling and the type of surface plays a serious role. The use of certain fall techniques can reduce the impact on the hip by more than 25%, thereby reducing the risk of hip fracture[36]. Furthermore it has been shown that the force of impact on the femoral neck can be reduced by almost 50% by adjusting the flooring system[37].

4.1.2 History of low-energy fracture

A low-energy fracture after 50 years of age increases the risk of a subsequent fracture approximately two-fold[38,39]. It has been reported that the majority of subsequent fractures occur in the first five years after an initial fracture[40]. This increased subsequent fracture risk was observed after virtually all types of low-energy fractures and persisted for up to 10 years depending on age and sex[40]. More recently, it has been reported that the risk of a subsequent fracture is highest shortly after the initial fracture[41]. Van Helden *et al.* reported an absolute subsequent fracture risk of 10.8% for any clinical fracture within two years after a previous fracture of which 60% occurred within one year[42]. Another study reported a 21% incidence of an identical subsequent fracture (hip, forearm, shoulder and vertebrae) within five years after the initial fracture, with the highest incidence immediately after the first fracture[43]. Silman proposed three possible explanations for the increased risk on subsequent fracture shortly following prior fracture[44]. First, risk factors provoking the first fracture might be still present and therefore increase the risk of a subsequent fracture. Second, the occurrence of fractures often results in immobilisation which provokes further bone loss and increased fracture risk. Third, mechanical influences caused by the initial fracture may result in difficulties in balance with an increased risk of falls and subsequent fractures.

4.1.3 Glucocorticoid therapy

Glucocorticoids play a major role in the treatment of asthma, inflammatory joint diseases and other diseases affecting the gastrointestinal tract and central nervous system. The prevalence of chronic oral glucocorticoid use has been estimated at 0.5% of the adult population. Among elderly (> 55 years), this number increases to 1.5%[45]. Use of glucocorticoids has been related to a decrease in BMD irrespective of the disease being treated. This decrease in BMD occurs predominantly in trabecular bone[46]. Fracture risk during oral glucocorticoid therapy is particularly increased in fractures of the vertebral body and proximal femur[47,48]. Furthermore the magnitude of this increase in fracture risk is directly related to the daily dose of glucocorticoids[47].

4.1.4 Family history of hip fracture

A history of fracture within a first degree relative, particularly a hip fracture in one of both parents, increases the risk of fracture significantly independent of BMD[49]. It is not clear how this relation can be explained, but a genetic predisposition has been suggested[49].

4.1.5 Cigarette smoking

It is well known that smoking is associated with a reduction in BMD. Furthermore, it has been shown that a history of smoking and current smoking increases the risk of hip fractures and fractures in general[50,51]. However, the risk is lower for subjects with a history of smoking compared to current smokers[50]. This suggests that the effect of smoking fades over time. Several mechanisms have been mentioned to explain the relation of smoking and fracture risk. For example, smoking women reach menopause earlier and smoker's tent to have lower body weight and, as a result, lower body mass index (BMI)[52].

4.1.6 Excessive alcohol consumption

An average alcohol intake of three or more units a day increases the risk of any fracture which is dose-dependent[53]. After correction for low BMD this relationship remains. Probably other aspects play a role like the increased risk of falling after alcohol consumption.

4.1.7 Low body weight

Low body weight, often defined as low BMI, is a well recognized risk factor for fractures[54,51]. This risk becomes most prominent with a BMI <20 kg/m^2 [54]. Weight gain above a BMI of 20 kg/m^2 has little protective effect. This means that obesity is not a protective factor but leanness itself is a risk factor[54]. Another aspect of importance is that the influence of BMI is markedly reduced after adjusting for BMD[55].

4.1.8 Secondary osteoporosis

As mentioned earlier, conditions like vitamin D deficiency or the use of certain medication can cause accelerated loss of bone tissue and is then referred to as secondary osteoporosis. A differentiation is made between rheumatoid arthritis and other factors associated with secondary osteoporosis. Secondary contributors to osteoporosis are present in 30-60% of the osteoporosis patients[11,56,57]

4.2 Psychological risk factors for fracture

4.2.1 Depression

In 2001, depressive disorders ranked number three of the leading causes of disease burden in high-income countries[58]. Considering the definition of depression, a distinction must be made between depressive syndrome and depressive symptoms. Depressive syndrome (major depression; MD) refers to the presence of at least one of the major signs of depression (low mood, or loss of interest) and at least four symptoms such as sleeping problems, cognitive dysfunction or eating problems (according to the DSM-IV classification). These symptoms have to be prominent for at least two weeks, with a major negative impact on daily activities. Patients with sub-threshold depression have symptoms of depression, but do not meet DSM-IV criteria for MD[59].

Low BMD and depression share biological etiological factors such as hypercortisolism[60]. Furthermore, both conditions have been associated with specific behavioural aspects like diminished physical activity and smoking[61]. Around 1990 the presence of depression in patients with osteoporosis was first noted[62].

Since then several studies investigated the relation between depression, bone density and fractures. A recent meta-analysis on this subject suggested an association between depression, increased fracture risk and low BMD[63]. These associations may be mediated by antidepressants[63]. A study which described the changes in depression up to one year in independently living older people who sustained fall-related injuries (80% fracture injuries), reported that depressive symptoms became manifest as recovery appeared to be delayed[64]. Another study assessed the development of MD over six months in elderly patients suffering from hip fracture[65]. The onset of MD was common after hip fracture, one out of every seven patients developed MD. Furthermore, it has been shown that depressed patients have poorer recovery after fracture[66,67].

4.2.2 Fear of Falling

Fear of falling is highly prevalent among middle-aged and older individuals[68,69], and is not necessarily restricted to those who have actually fallen[70]. It has found to be associated with adverse consequences such as reduced activity levels[68-70], and progressive loss of health-related quality of life[71]. Furthermore, fear of falling has been related to depressive disorder, symptoms of depression and feelings of anxiety[70,72,73]. Moreover it has been shown that falls not only increases fear of falling, a reversed relation was also found: fear of falling increased the number of falls[74]. While Friedman *et al.* showed that the combination of fear and increased numbers of falls eventually leads to functional decline, Luukinen *et al.* emphasized the link between fear of falling and increased risk for fracture-causing falls in older adults [74,75].

5. MANAGEMENT OF FRACTURE RISK

With regard to case-finding of subjects at high risk for fractures, several instruments have been designed. The Dutch guidelines for osteoporosis are aimed at prevention, diagnosis and treatment of osteoporosis and were published in 2002[76]. In this guideline, fracture risk was assessed based on eight specified clinical risk factors (table 1). In patients with an increased fracture risk (determined as a risk score ≥ 4 points, based on the eight clinical risk factors with a risk-score per item) BMD measurements are advocated. Pharmacological treatment is advised to subjects with a low T-score (≤-2.5 SD) and/or the presence of one or more vertebral fractures. In the new Dutch guideline for osteoporosis and fracture prevention, that will be available in 2011, available only in concept at present, the same clinical risk factor strategy is followed as in the 2002 guideline, with 3 additional risk factors (*i.e.* rheumatoid arthritis, secondary osteoporosis, and a fall within the last 12 months) and with more emphasis on additional assessment in patients presenting with a recent fracture and in patients at high risk for vertebral fractures.

Table 1 *Clinical risk factors and scores according to the Dutch guidelines (2002). Dual energy X-ray Absorptiometry (DXA) measurement is recommended at a total risk score ≥4*

Risk factor	score
Vertebral fracture	4
Long-term use of high-dose corticosteroids (>3 months; >7.5 mg/day)	4
Fracture after age of 50 years	4
Age > 70 years	2
Age > 60 years	1
Hip fracture in first-degree family member	1
Weight < 60 kg	1
Immobility	1

6. AIMS AND OUTLINE OF THE THESIS

In this thesis several aspects of fracture risk in Primary care patients are studied. In chapter 2, the prevalence of vertebral fractures is studied in subjects with clinical risk factors for fractures in Primary care. In chapter 3, the measurement properties of the Activities-specific Balance Confidence Scale (ABC16) in patients aged 50 years and older with a recent low-energy fracture are assessed.

In chapter 4, 5 and 6, patients with a recent low-energy fracture are prospectively studied with regard to the prevalence and incidence of depression after a recent fracture (chapter 4), the relation between depression and fall incidents (chapter 5) and the ability to predict subsequent fractures using the fracture risk calculator models FRAX® and Garvan (chapter 6).

Chapter 2

The identification of vertebral fractures is important for decisions on fracture prevention. Vertebral fracture assessment (VFA) was shown to be a patient-friendly and valid method for detecting undiagnosed vertebral fractures in (Dutch) women. However, this has only been investigated in women seeking care at secondary or tertiary institutions. The purpose of the study was to investigate the prevalence of previously undiagnosed vertebral fractures using the VFA technique in women aged 50 years and older with one or more clinical risk factors in Dutch Primary care. Furthermore the implications of these outcomes on fracture risk management are discussed.

Chapter 3

Fear of falling is highly prevalent among older individuals and has been suggested to increase the risk for fracture-causing falls. It seems apparent that fracture prevention programs should thus, next to clinical risk factors, focus on the presence of fear of falling. Validation of a tool for measuring fear of falling in a high risk population is important, as it will assist in optimizing screening protocols for those at risk for future fractures. This study examines the measurement properties of the Activities-specific

Balance Confidence Scale (ABC-16), which was developed to assess an individual's perception of balance confidence, (often used as a measure of fear of falling).

Chapter 4

In several studies depression has been associated with increased fracture risk and decreased BMD. From a biological point of view, it is believed that hyperactivity of the hypothalamic pituitary-adrenal (HPA) axis and resulting hypercortisolism can explain this association. From a behavioural perspective, it has been suggested that poor life style, including physical inactivity, nutritional deficiency, excessive alcohol use and smoking (which are all common in patients suffering from depression) may negatively affect bone strength and therefore increase the risk of falls and fractures. Moreover, the association between osteoporosis, fractures and depression could be mediated by the use of psychotropic drugs. From a scientific point of view, observational research regarding the occurrence of major depression (MD) after low-energy fractures is important for gaining more insight into the explanatory mechanisms of the relation between depression, fractures and BMD. The objective of the study described in chapter 4 was to investigate the prevalence and incidence of a major episode of depression during 12 months of follow-up in women aged 50 years and older who suffered from a recent low-energy fracture. We hypothesised that MD occurred more frequently in women who sustained a recent fracture compared to women in the general population and that, in particular, women with a history of depression would be at risk for developing a new episode of MD after a low-energy fracture.

Chapter 5

Falls are a strong and independent risk factor for fractures in elderly people. It has been reported that up to 70% of low-energy fractures are caused by a fall and 19% of women with a recent low-energy fracture reported another fall within 3 months after fracture. Depression has been described as a potential risk factor for falls in various samples and settings, however its relation has not been described in women who suffered from a recent low-energy fracture. The purpose of this study was to investigate the relation between depression and fall incidents in post-menopausal women with a recent low-energy fracture.

Chapter 6

A history of a fracture significantly increases the risk of subsequent fractures at other skeletal sites. The risk of a subsequent fracture is highest shortly after the initial fracture. The Garvan nomogram has been developed to assess five- and 10-year fracture risk while FRAX® only takes 10-year fracture risk into account. As fracture risk assessment is important in the period following a fracture, this study was aimed to assess the applicability of both fracture risk calculators on short term fracture risk in women aged 60 years and older who had recently suffered from a low-energy fracture.

Chapter 7

In chapter 7 the main findings of the studies are summarized and discussed. Additionally, possible clinical implications and recommendations for future research are proposed.

Two projects in Primary health care were conducted. The first project aimed at the prevalence of a vertebral fracture in Primary care, the second project is called the Eindhoven Subsequent Fracture and Osteoporosis Reduction project (ESFOR-p). The research designs of these projects will be discussed below.

7. RESEARCH DESIGN

7.1 Prevalence of vertebral fracture in Primary care

Between July 2007 and September 2009, participants were recruited through advertisements in local newspapers and flyers in Dutch general practices, describing the case-finding strategy according to the Dutch guidelines for osteoporosis (table 1). Participants were able to register themselves at the participating general practices. After registration, participants received an invitation for Dual energy X-ray Absorptiometry (DXA) and Vertebral Fracture Assessment (VFA) including an information letter about the study. During their appointment at the general practice, BMD and the presence of vertebral fractures were determined. Furthermore, the clinical risk profile according to the Dutch guidelines for osteoporosis was assessed. According to the guideline, women with a T score ≤ -2.5 SD and/or with one or more vertebral fractures, who were eligible for treatment with anti-osteoporosis medication, were advised by their general practitioner. A total of 629 women registered for participation. Two women were excluded due to an age below 50 and 10 women did not sign informed consent. Therefore 617 women were included in this study of whom the characteristics are shown in table 2. This study was approved by the Medical Ethical Committee of the Máxima Medical Centre Veldhoven (the Netherlands).

Table 2 *Characteristics of the women in the vertebral fracture assessment study (N=617)*

	Mean		SD	N	%
Age		68.92	8.70		
DXA outcome	Osteoporosis			122	20
	Osteopenia			260	42
	Normal BMD			235	38
Risk factors	Weight (kg)	71.09	13.78		
	BMI (kg/m^2)	27.08	5.14		
	History of vertebral fracture			28	5
	History of fracture ≥50 year			300	49
	Parental history of hip fracture			162	26
	Use of high-dose corticosteroids*			58	9
	Immobility			101	16

* (>3 months; >7.5 mg/day)

7.2 ESFOR-p

Between October 2006 and July 2008 all eligible patients of the fracture and osteoporosis outpatient clinic (F&O clinic) of two teaching hospitals in the south-east of the Netherlands were invited to participate in a prospective cohort study on the effects and processes of osteoporosis and subsequent fractures, called the Eindhoven Subsequent Fracture and Osteoporosis Reduction-project (ESFOR-p). Participants were found eligible if they were aged 50 years and older and sustained a recent low-energy fracture (defined as resulting from a fall from standing height or lower). After primary fracture care all patients were invited for BMD measurement and further clinical evaluation by a specialised nurse.
During the period of inclusion, 738 patients aged 50 years and older, who visited the F&O clinic, were interested to participate (figure 2). They were informed about the project in more detail through an information letter. Two weeks after their visit at the F&O clinic, interested patients were contacted by telephone by one of the researchers to provide detailed information regarding the study and to obtain their final decision whether or not they would participate.

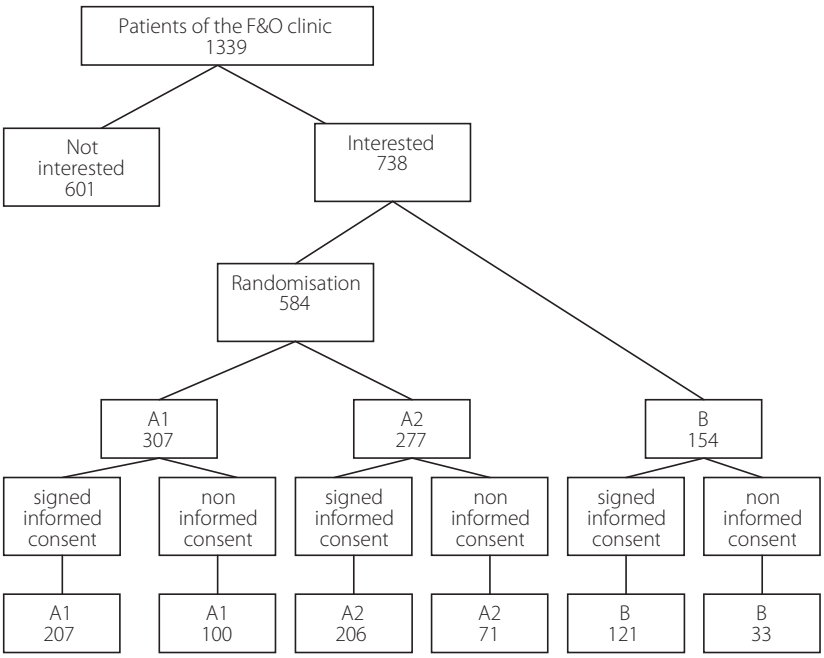

Figure 2 *Flowchart of participation in ESFOR-p*

Participants with insufficient knowledge of the Dutch language (unable to read/comprehend Dutch language) or impaired cognitive abilities (*i.e.* pre-dementia) were excluded. A total of three groups were composed (figure 2). Participants with low BMD (osteoporosis or osteopenia) were randomly divided into two groups: an intervention group (A1) and a control group (A2). Participants with a normal BMD

were allocated in a separate control group (B). Participants in the intervention group were visited by researchers every six months, and were telephonically contacted in between the visits, during a period of maximum two years. At the visits, information regarding risk factors and psychosocial consequences of the fracture was collected using standardized interviews, tests and questionnaires. Subjects of the control groups received the same set of questionnaires by mail, with an interval of 12 months, three times at most. The ESFOR-p study was approved by the Medical Ethical Committee of the Máxima Medical Centre Veldhoven (the Netherlands).

As shown in figure 2, a total of 1339 patients of 50 years and older with a low-energy fracture visited the F&O clinics (mean age 66 years (SD=9.5); 40% was diagnosed with osteoporosis, 37% with osteopenia and 22% had a normal BMD). Of the 738 patients who were interested in participation in ESFOR-p (mean age 66 years (SD=8.7); 42% osteoporosis, 36% osteopenia and 21% normal BMD), finally 534 patients met the inclusion criteria and signed informed consent (characteristics are shown in table 3). In figure 3, a flowchart of the follow-up is given. During the first and second year of follow-up 75 and 22 participants respectively dropped out (14% and additional 7%).

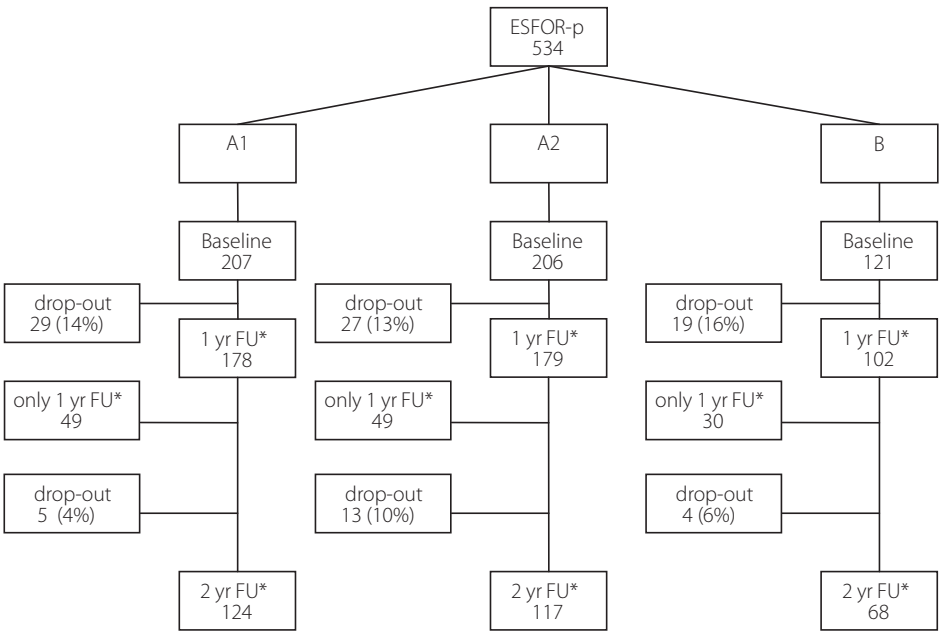

Figure 3 *Flowchart of the follow-up in ESFOR-p*

* 1 yr FU=one year follow-up; 2 yr FU=two year follow-up

Table 3 *Characteristics of the participants in ESFOR-p (N=534)*

		Mean	SD	N	%
Sex	Women			441	83
	Men			93	17
Age		66	9		
Race	Caucasian			529	99
	Other			5	1
Educational level	Low			278	52
	Moderate			198	37
	High			58	11
Social status	Married/ living together/LAT*			390	73
	Widowed/ divorced			144	27
Economic status	Low (< €1000/month)			158	30
	Moderate (€1000-3000/month)			342	64
	High (>€3000/month)			34	6
Type of fracture	Hip fracture			47	9
	Vertebral fracture			27	5
	Wrist fracture			145	27
	Other fractures[a]			311	58
	Multiple fractures[b]			4	1
DXA* outcome	Osteoporosis			222	42
	Osteopenia			193	36
	normal BMD*			119	22
Risk factors	Weight (kg)	72	13		
	BMI* (kg/m^2)	26	4		
	Parental history of hip fracture			96	18
	Current smoking			81	15
	Use of high-dose corticosteroids[c]			21	4
	Rheumatoid arthritis			35	7
	Alcohol units ≥3/day			46	9
Psychological characteristics	Depressive symptoms (≥12 points)			92	17
	Fear of falling (<80% confidence)			178	33

*BMD=bone mineral density, BMI=body mass index, DXA=dual energy X-ray absorptiometry, LAT=living apart together

[a] hand, forearm, elbow, clavicle, ankle, foot.

[b] 1x hip and vertebral fracture; 1x vertebral and wrist fracture; 1x wrist and vertebral fracture; 1x wrist and other fracture.

[c] (>3 months; >7.5 mg/day)

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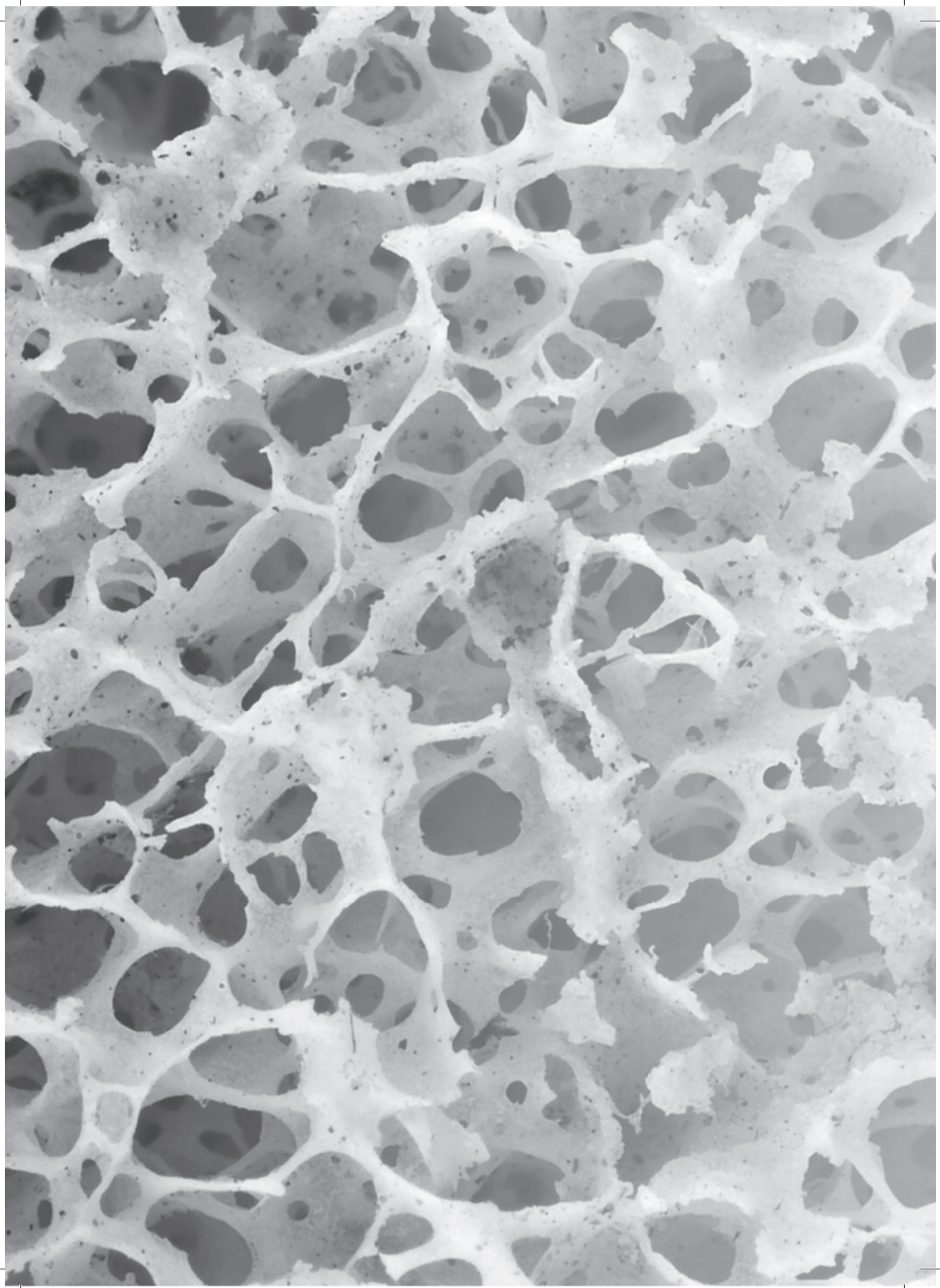

Chapter 2

Vertebral fractures in women aged 50 years and older with clinical risk factors for fractures in Primary care

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ABSTRACT

Background: The identification of vertebral fractures (VFs) is important for decisions on fracture prevention. Vertebral fracture assessment (VFA) was shown to be a patient-friendly and valid method for detecting undiagnosed VFs in (Dutch) women. However, this has only been investigated in women seeking care at secondary or tertiary institutions.

Objective: To investigate the prevalence of previously undiagnosed VFs in women in Dutch Primary care using VFA.

Study design: A total of 566 Dutch women aged 50 years and older (mean age, 69 years; SD = 8.4) with clinical risk factors (CRFs) for fractures volunteered for dual-energy X-ray absorptiometry (DXA) measurement and VFA. VFs were defined semi-quantitatively using Genant's method.

Results: One CRF was present in each of 130 women, 274 had two, and 162 women had more than two CRFs. In 120 (21%) of the women, previously unknown osteoporosis (T-score ≤ -2.5 SD) was diagnosed, and in 174 (31%), a previously undiagnosed moderate or severe VF was found. No osteoporosis was found in 130 (75%) of the women with a VF. Based on the outcome of DXA, 21% of the women were eligible for treatment, while the combination of DXA and VFA resulted in a total of 250 (44%) women requiring treatment.

Conclusions: The percentage of previously unknown VFs diagnosed by VFA in women aged 50 years and older with one or more CRFs for fractures in Primary care is high. When only using BMD measurements, only half the women eligible for treatment would actually receive this. We recommend performing VFA in all women aged 50 years and older who are referred for DXA based on Dutch case finding criteria.

Keywords: osteoporosis, vertebral fracture, VFA, Primary care, bone densitometry, DXA

INTRODUCTION

During a person's lifetime, osteoporotic fractures affect one out of two women and one out of five men[1]. While society is faced with increasing costs resulting from fractures, individuals are affected by morbidity, mortality and decreased quality of life[2]. Patients at risk for osteoporotic fractures are mainly identified by the assessment of clinical risk factors (CRFs) and bone densitometry[3]. An important and independent risk factor for future fractures is vertebral fractures (VFs). Almost 20% of women who sustain a VF will suffer a further one the following year[4]. After a first VF, the risk of subsequent VFs is increased three to five fold, and the risk of a non-VF (including hip fractures) is increased two-fold[5]. Since only one in three VFs presents with acute signs and symptoms, accurate diagnosis requires imaging of the spine[6]. Spine X-rays are considered the gold standard[7]. Research has shown that a high percentage (21%) of undiagnosed VFs was identified in women in Primary care using spinal radiographs[8]. Recently, another method of detecting VFs has been introduced: vertebral fracture assessment (VFA). This can be performed with the same device as Dual Energy X-ray Absorptiometry (DXA), and enables the combined assessment of bone mineral density (BMD) and VFs. Compared to spinal X-rays, the radiation dose is lower, leading to higher patient convenience and cost-effectiveness[9-11]. Comparable to the detection rate of VFs by spinal X-rays, VFA has proved to be a valid and patient-friendly technique for diagnosing VFs[10-12].

The identification of VFs is an important aspect of fracture prevention in Primary care[8]. Therefore, the aim of this study is to investigate the prevalence of previously unknown VFs in women aged 50 years and older in Dutch Primary care using VFA, and to discuss its impact on fracture risk management.

METHODS

Subjects

Between September 2006 and June 2007, participants were recruited by means of advertisements in local newspapers and flyers left in Dutch general practices, which described a case-finding strategy according to the Dutch guidelines for osteoporosis, based on a list of CRFs for fractures with a risk-score per item (table 1)[13]. Women aged 50 years and older with self-reported CRFs, who were not being treated for osteoporosis nor had suffered from a previously diagnosed VF, were invited for DXA and VFA assessment, which was covered by their health insurance. The invitation to participate was based on self-registration, regardless of risk score. However, only women with at least one CRF were eligible.

According to the Dutch guidelines from 2002, women with a T-score ≤ -2.5 SD and/or with one or more VFs were eligible for treatment[13]. A total of 629 women registered for participation. Two women were excluded due to being aged less than 50, 23 women failed to report at least one CRF for fractures, and ten women did not sign the informed consent. Furthermore, 28 women reported a history of VF. These women were excluded from the analysis for reasons of clarity. Therefore, analyses were carried out in 566 women (mean age, 69 years; SD = 8.4). The study was approved by the medical ethical committee of the Máxima Medical Centre Veldhoven, the Netherlands, and was carried out in accordance with the Declaration of Helsinki.

Table 1 *Dutch case-finding instrument for dual energy X-ray absorptiometry measurement: recommended if total risk score ≥4*

Risk factor	score
Vertebral fracture	4
Long-term use of high-dose corticosteroids (>3 months; >7,5 mg/day)	4
Fracture after age of 50 years	4
Age > 70 years	2
Age > 60 years	1
Hip fracture in first-degree family member	1
Weight < 60 kg	1
Immobility	1

Measurements

During the appointment for BMD measurement and VFA, participants' clinical risk profiles were evaluated according to the Dutch guidelines for osteoporosis[13], including the following risk factors: long-term use of high doses glucocorticoids (> 3 months, > 7.5 mg prednisone equivalent/day), a previous history of fracture after age 50, age, a history of hip-fracture in a first-degree relative, low body weight (<60 kg), body mass index (BMI), and immobility (less than 15 minutes a day physical activity).

BMD and VFA were measured using a Hologic W DXA system. The DXA scans were obtained by one well-trained professional applying the standard procedures supplied by the manufacturer for scanning and analysis. Measurements made at the lumbar spine, total hip and left femoral neck were used for assessing BMD. In accordance with the World Health Organization (WHO) classification[14], osteoporosis was defined as a T-score ≤ -2.5 SD, osteopenia as a T-score < -1.0 and > -2.5 SD, and normal BMD as a T-score ≥ -1.0 SD. Genant's semi-quantitative method was used to define VFs as mild (20-25% compression), moderate (25-40% compression), or severe (>40% compression)[15]. With radiography as gold standard, sensitivity and specificity of VFA, were reported to be 62.5-78.6 and 93.1 respectively, for the presence of one or more moderate or severe VFs[10]. Sensitivity increased with a higher prevalence of VFs[10]. Based on these findings, and the fact that moderate and severe VFs show the best predictive value for future fractures[10,16,17], we only considered moderate and severe VFs in this study. Mild vertebral compression was not considered a VF. Furthermore, a distinction was made in fracture site (thoracic spine or lumbar spine) and type of fracture (wedge, biconcave or crush).

Statistical analyses

Descriptive statistics were used to assess the rate of VFs, as was the consensus of fracture management based on DXA and VFA. Women with osteoporosis and those with ≥ 1 VFs were considered eligible for treatment. Chi-square, Student's t-tests and when appropriate with respect to skewed distribution of continuous data, Mann-Whitney U tests were used to assess statistical differences between women with and without VFs ($p < 0.05$). A multiple logistic regression analysis was performed to investigate the relevance of the number of CRFs present for unknown VFs, after controlling for age, BMI, the use

of glucocorticoids, a history of previous fracture after age 50, hip fracture in a first-degree relative, and immobility. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS Statistics) version 18.0.

RESULTS

The characteristics of the population, including the results of DXA and VFA, are presented in table 2. Of 7358 vertebrae, 267 (3.6%) were classified as unreadable, with 248 (93%) of the unreadable vertebrae located in T4-T6 and 19 (7%) from T7 to L4. Mild VFs were present in 44% of the patients without a moderate or severe VF, and in 64% of the patients who were classified as having a VF based on the presence of moderate or severe VFs. As for CRFs according to the Dutch guidelines: 54 women (10%) had used high doses of glucocorticoids for more than three months, 282 (50%) reported a history of fracture after age 50, 272 (48%) were aged >70 years, while a further 208 (37%) were aged 61-70 years. Hip fracture in a first degree relative was reported by 153 (27%) of the women and 119 (21%) weighed less than 60 kg. Furthermore, 100 (18%) women described their level of daily exercise as meeting the conditions for immobility. In total, 130 (23%) women met the criteria for one risk factor, 274 (48%) reported two risk factors, 141 (25%) fulfilled the criteria for three risk factors, 18 (3%) had four risk factors, and 3 (<1%) women fulfilled the criteria for five risk factors.

As presented in table 2, 120 (21%) women, 44 with and 76 without VF, were diagnosed with osteoporosis based on the DXA measurement, and were thus eligible for treatment according to the Dutch guidelines. Based on VFA, 174 (31%) women had one (70%) or more (30%) moderate or severe VFs. Of these, 163 (94%) had a moderate fracture, while 11 (6%) had a severe fracture. One hundred and forty-one (81%) VFs were classified as wedge, 25 (14%) as biconcave, and eight (5%) as crush fractures. One hundred and thirty-five (78%) fractures were found in the thoracic spine and 39 (22%) in the lumbar spine. Considering fracture type, women with a wedge fracture were significantly younger compared to women with a biconcave or crush fracture (Mann W-U, $p = .008$). No significant differences were found in participant characteristics or CRFs with respect to fracture site (thoracic versus lumbar).

Of the 174 women with a VF, 44 (25%) were diagnosed with osteoporosis. Thus, using VFA, 130 women were eligible for treatment based on the presence of one or more VFs in addition to those identified by DXA measurement as having osteoporosis (table 3). The total number of women eligible for treatment based on combined DXA ($n = 120$) and VFA ($n = 130$) was 250 (44%). Additional analyses showed that women with one or more VF were significantly older (Mann W-U, $p = .002$), had a higher BMI (Mann W-U, $p = .007$), showed lower BMD and T-scores of the femoral neck (Mann W-U, $p = .003$ and Mann W-U, $p = .002$ respectively), lower BMD and T-scores of the total hip (Mann W-U, $p = .021$ and Mann W-U, $p = .016$ respectively), and more often presented with one risk factor compared to the more common presence of two risk factors in women with no VFs ($chi^2 = 6.4$, $df = 1$, $p = .011$). Furthermore, with respect to the 130 women who were eligible for treatment by using VFA in addition to those identified by DXA measurement alone, the women with osteopenia had a significantly lower BMI (Mann W-U, $p = .009$), and a lower BMD of the lumbar spine, the femoral neck and the total hip (Mann W-U, $p = <.001$, Mann W-U, $p = <.001$ and Mann W-U, $p = <.001$ respectively) compared to the women with a normal BMD.

Table 2 *Baseline characteristics, clinical risk factors and BMD[a] in 174 women over 50 years with VF[a] and 392 women without VF assessed by VFA[a†]*

Characteristic		VF[a] (n=174) n (%)	No VF[ab] (n=392) n (%)	*p*	
				X^2	Mann W-U
Demographics					
Age		71.5 (52-91)	69.0 (50-89)		.002
BMI[a]		27.1 (16.9-43.4)	26.0 (15.9-47.5)		.007
Fracture risk factors					
Use of glucocorticoids[c]		17 (10)	37 (9)	1.000	
Fracture after age 50		91 (52)	191 (49)	.488	
Age >70		96 (55)	176 (45)	.030	
Age 61-70		58 (33)	150 (38)	.304	
Hipfracture first-degree relative		39 (22)	114 (29)	.122	
Weight <60 kg		31 (18)	88 (22)	.256	
Immobility		23 (13)	77 (20)	.084	
Number of risk factors according to Dutch guidelines					
1		51 (29)	79 (20)	.023	
2		72 (41)	202 (52)	.032	
3		46 (26)	95 (24)	.650	
4		3 (2)	15 (4)	.291	
5		2 (1)	1 (<1)	.469	
Risk score		5.0 (1-12)	4.5 (1-11)		.549
BMD outcome					
Diagnosis[d]	Normal BMD	55 (32)	149 (38)	.171	
	Osteopenia	75 (43)	167 (43)	.985	
	Osteoporosis	44 (25)	76 (19)	.141	
Lumbar spine	BMD	0.91 (0.30-1.58)	0.92 (0.54-1.56)		.487
	T-score	-1.2 (-4.5-4.9)	-1.1 (-4.7-4.6)		.715
	Z-score	0.75 (-2.5-7.4)	0.80 (-2.8-6.9)		.933
Femoral neck	BMD	0.66 (0.34-1.03)	0.69 (0.37-1.54)		.003
	T-score	-1.7 (-4.6-1.4)	-1.5 (-4.3-6.2)		.002
	Z-score	0.20 (-2.3-2.8)	0.20 (-2.3-8.5)		.078
Total hip	BMD	0.82 (0.29-1.22)	0.85 (0.52-1.76)		.021
	T-score	-1.00 (-5.3-1.6)	-0.80 (-3.5-6.7)		.016
	Z-score	0.60 (-3.3-3.6)	0.60 (-2.3-7.5)		.179

[†] Continuous data are presented as median (range)

[a] BMI=Body Mass Index, BMD=Bone Mineral Density, VF=Vertebral Fracture(s), VFA=Vertebral Fracture Assessment.

[b] Including women with a mild fracture (in accordance with the semi-quantitative method of Genant)

[c] > 3 months; > 7,5 mg/day

[d] Diagnosis based on BMD of the lumbar spine, femoral neck and total hip

Table 3 *Baseline characteristics, clinical risk factors and BMD[a] in 131 women over 50 years with VF[a] assessed by VFA[a] in addition to those identified by DXA[a] measurement alone, with regard to normal bone mineral density and osteopenia[†]*

Characteristic		Normal BMD[a] (n=55) n (%)	Osteopenia (n=75) n (%)	*p*	
				X^2	Mann W-U
Demographics					
Age		70 (52-91)	70 (54-90)		.294
BMI[a]		29.0 (19.9-43.4)	27.2 (19.5-40.9)		.009
Fracture risk factors					
Use of glucocorticoids[b]		8 (15)	6 (8)	.366	
Fracture after age 50		26 (47)	42 (56)	.420	
Age >70		26 (47)	37 (49)	.956	
Age 61-70		21 (38)	29 (39)	1.000	
Hipfracture first-degree relative		13 (24)	19 (25)	.987	
Weight <60 kg		3 (5)	9 (12)	.333	
Immobility		8 (15)	13 (17)	.853	
Number of risk factors according to Dutch guidelines					
1		19 (35)	23 (31)	.781	
2		24 (44)	28 (37)	.587	
3		11 (20)	21 (28)	.401	
4		-	2 (3)	NA[a]	
5		1 (2)	1 (1)	1.000	
Risk score		4 (1-10)	5 (1-12)		.458
BMD outcome					
Lumbar spine	BMD	1.04 (0.30-1.58)	0.90 (0.78-1.26)		<.001
	T-score	0.00 (-1.0-4.90)	-1.30 (-2.40-1.90)		<.001
	Z-score	2.00 (-0.60-7.40)	0.60 (-0.70-4.70)		<.001
Femoral neck	BMD	0.75 (0.63-1.03)	0.65 (0.52-0.93)		<.001
	T-score	-0.60 (-1.0-1.40)	-1.80 (-2.40-0.0)		<.001
	Z-score	0.95 (-0.90-2.8)	0.20 (-1.60-1.90)		<.001
Total hip	BMD	0.95 (0.82-1.22)	0.80 (0.65-1.13)		<.001
	T-score	0.00 (-1.0-1.6)	-1.20 (-2.4-0.70)		<.001
	Z-score	1.50 (-0.2-3.6)	0.55 (-1.0-1.9)		<.001

[†] Continuous data are presented as median (range)

[a] BMI=Body Mass Index, BMD=Bone Mineral Density, DXA=Dual Energy X-ray Absorptiometry, NA=non applicable, VF=Vertebral Fracture(s), VFA=Vertebral Fracture Assessment.

[b] > 3 months; > 7,5 mg/day

According to the multiple logistic regression analysis, the number of CRFs did not significantly affect the risk of a VF, after controlling for age, BMI, the use of glucocorticoids, a history of previous fracture after age 50, hip fracture in a first-degree relative, and immobility (table 4). However, BMI had a significant effect on the presence of a VF (O.R . = 1.23, 95% C.I. = 1.02-1.49).

Table 4 *Results of multiple logistic regression analysis in 566 women, dependent variable: vertebral fracture*

Variable	Odds ratio[†]
Age >70	1.41 (0.95-2.10)
BMI[a]	1.23 (1.02-1.49)
Use of glucocorticoids[b]	0.93 (0.45 - 1.93)
Fracture after age 50	0.97 (0.58 - 1.63)
Hipfracture first-degree relative	0.74 (0.41 - 1.32)
Immobility	0.56 (0.29 - 1.07)
Number of risk factors according to Dutch guidelines	1.07 (0.71 - 1.61)

[†] Associations are presented as odds ratio (95% confidence interval).
[a] BMI was transformed into quartiles to compensate for skewness of the data: 15.93 - 23.53 (n=142); 23.54 - 26.22 (n=142); 26.23 - 29.54 (n=141); 29.55 - 47.48 (n=141)
[b] > 3 months; > 7,5 mg/day

DISCUSSION

This study has shown a high percentage of previously unknown VFs (31%) in women aged 50 years and older (mean age, 69 years; SD=8.4) with CRFs in Primary care who volunteered for DXA and VFA after invitation. Of the women with a VF, 75% had no osteoporosis according to the WHO definition. Up until now, it was common practice, as advised in the 2002 Dutch guidelines, to evaluate the need for treatment for preventing fractures based on BMD outcome and in the presence of a VF, but there were no guidelines on how, when, and in whom to diagnose VFs[13]. Based on a T-score ≤ -2.5 SD of the femur or the lumbar spine, 21% of the women in our Primary care study were eligible for treatment, while using VFA, 130 women were also identified, based on the presence of a VF. Thus, 250 compared to 120 women required treatment when VFA was added to the DXA, suggesting a more than two-fold increase. This study emphasises the need for systematically performing VFA in women referred for DXA measurement in Primary care patients.

Previous studies also reported a high prevalence of VFs (25-39%) in women aged over 50 years[6,18-20]. Jager *et al.* recently reported a prevalence of 20% VFs in Dutch women using VFA[12]. The higher percentage of VFs in our study could be explained by the fact that we only included women aged 50 years and older (mean age, 69 years; SD = 8.4), while Jager *et al*. included consecutive patients referred for BMD testing, and the 65% women in their study had a mean age of 54 years, range 18-94 years[12]. Our results suggest that the presence of VFs is not limited to women seeking care at secondary or tertiary institutions, but is also highly prevalent in Primary care. This has also been reported by Netelenbos *et al.* who investigated

the percentage of VFs in Dutch Primary care women[8]. They included women aged over 60 years (mean age, 71 years) with no osteoporosis but with CRFs, and discovered VFs in 21% of the women. Compared to these results, we found a higher percentage of VFs in women with no osteoporosis (29%). This could be explained by the fact that Netelenbos *et al*. used a different set of CRFs to select the women for further examination[8]. Moreover, they used spinal radiographs to diagnose VFs. The rate of false positives could be higher in VFA compared to spinal radiographs, especially in the thoracic region, and therefore this could also in part be an explanation for the differences between the percentage of VFs in both Dutch populations[21]. However, a study to the accuracy of VFA in detecting moderate and severe VFs according to Genant's semi-quantitative method showed that the rate of false positives was low[10], which makes the difference in selection strategies a more likely explanation.

Furthermore, we found that women with VF had significantly lower T-scores at the total hip and the femoral neck of the hip than women without VF. However, no significant differences were found for the T-score of the lumbar spine. A possible explanation might be that a VF due to osteoporosis increases lumbar spine BMD and falsely suggests improved skeletal status[22].

Another notable finding is that, on average, women with VFs had a significantly higher BMI than women without VFs, while a reversed relationship has often been described[23]. However, Pirro *et al.* recently reported an increased risk of VFs in postmenopausal women with high BMI[24]. With respect to fracture type, women with a wedge fracture were younger compared to women with a biconcave or crush fracture. Our results are in line with the European Prospective Osteoporosis Study that reported an effect of age to increase incident fracture size. Furthermore subsequent fractures were reported to be significantly larger when the initial fracture was a biconcave or crush fracture[25].

Finally, the number of CRFs present did not affect the risk of VF in our research sample. According to tools such as the FRAX, which have been designed to estimate fracture risk based on the presence of CRFs, fracture risk increases when more CRFs are identified. A possible explanation for our finding could be that the specific CRFs included in the Dutch case-finding method are not very sensitive for identifying subjects at high risk for fractures, since it has already been shown that this method is not very sensitive when selecting patients with osteoporosis[26]. However, the aim of this study was to asses the prevalence of unknown VFs in women aged 50 years and older in Primary care. The evaluation of the predictive value of case finding methods for identifying subjects with unknown VFs is beyond the scope of this paper.

This study has several limitations. Since the participants responded to advertising strategies and, according to the Dutch guidelines, only women with at least one CRF were included, a selection bias could have occurred. This could be reflected by the high number of corticosteroid users in the study population (10%), as well as the high number of patients with a history of fracture (50%). As a result, the prevalence of VFs in the current study may not be applicable to the general population. However, this was not the aim of the study. Despite this limitation, our results emphasise that previously unknown VFs are present in a substantial number of Primary care women with CRFs, and that this finding is not limited to populations seeking care at secondary or tertiary institutions. A further limitation of this study is that the use of VFA is limited in the upper thoracic levels, due to overlying ribs and vascular structures. However,

in this area, interpretation and image quality of radiographs are also diminished and the incidence of VF is less common[8]. Furthermore, we only investigated CRFs according to the Dutch guidelines. Several risk factors that are currently implemented in FRAX, a common used algorithm for fracture risk assessment, were therefore not included for fracture risk assessment in this study[27]. Age, long term use of high-dose corticosteroids, weight, a previous fracture and a hip fracture in a first-degree family member are incorporated in FRAX and the Dutch guidelines, but in different ways. FRAX uses age and weight as a continuous variable while the Dutch guidelines use a cut-off level (table 1). Regarding corticosteroid use, FRAX implemented a smaller daily dose of corticosteroid use as CRF compared to the Dutch guidelines. Furthermore, the definition of a previous fracture and hip fracture in a first degree family member differ between both instruments. In addition to the Dutch guidelines, FRAX implemented CRFs such as current smoking, the presence of rheumatoid arthritis and secondary osteoporosis, three or more units of daily alcohol use and BMD. Considering the indications for VFA according to the International Society for Clinical Densitometry, historical height loss is another aspect which is lacking in the Dutch guideline[28].
From the present study, it can be concluded that the prevalence of previously unknown VFs diagnosed with VFA in women aged 50 years and older with CRFs in Primary care, is unexpectedly high. When using BMD measurements only, only half the women eligible for treatment would actually receive this. We recommend performing VFA in all women aged 50 years and older who are referred for DXA based on Dutch case finding criteria.

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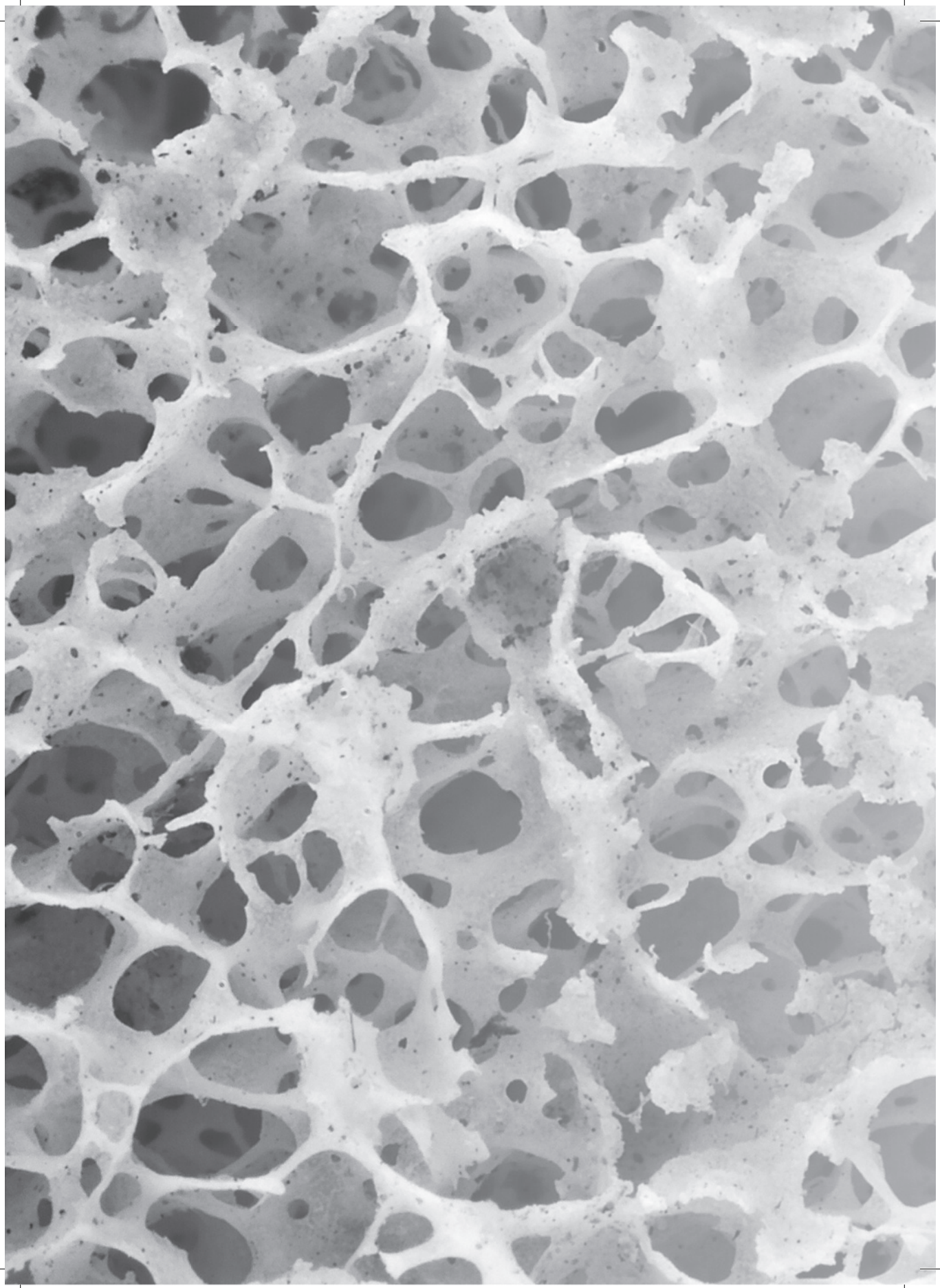

Chapter 3

Measurement properties of the activities-specific balance confidence scale in subjects aged 50 years and older at risk for future fractures

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ABSTRACT

Purpose: Fear of falling is related to increased numbers of falls, and elevates the risk for fractures. The Activities-specific Balance Confidence Scale (ABC16) is a commonly used questionnaire for assessing fear of falling, and has not yet been validated in patients with fractures. The study, therefore, set out to validate the ABC16 in patients aged 50 years and older who were suffering from low-energy fractures.

Methods: 460 participants aged 50 years and older completed a questionnaire package including the ABC16, SF36 Health Survey (SF36), Edinburgh Depression Scale (EDS), and the anxiety subscale of the Symptom Checklist 90 (SCL90). Structural coherence, internal consistency, and construct validity of the ABC16 were determined.

Results: Principal component analysis indicated a one component structure, with factor loadings ≥ 0.67. Internal consistency of the ABC16 was high: Cronbach's alpha = 0.95. Regarding construct validity, the ABC16 showed significant relations with quality of life, depression and anxiety ($r = 0.46$, $p < 0.001$; $r = -0.43$, $p < 0.001$; $r = -0.37$, $p < 0.001$).

Conclusions: The ABC16 showed good measurement properties. It constitutes a psychometrically sound screening tool for identifying middle-aged and older patients with balance confidence problems who are at risk for future fractures.

Keywords: balance confidence; measurement properties; fracture

INTRODUCTION

Fear of falling is highly prevalent among middle-aged and older individuals[1,2], and is not necessarily restricted to those who have actually fallen[3]. Fear of falling has been found to be associated with adverse consequences such as reduced activity levels[1-3], increased number of falls[4] and progressive loss of health-related quality of life[5]. Furthermore, fear of falling has been related to depressive disorder, symptoms of depression and feelings of anxiety[3,6,7]. While Friedman *et al.*[4] showed that the combination of fear and increased numbers of falls eventually leads to functional decline, Luukinen *et al.*[8] emphasized the link between fear of falling and increased risk for fracture-causing falls in older adults. An estimated 5 to 10% of falls result in a fracture[9,10], and roughly 70% of fractures are caused by a fall[11].

In recent years, the insight that both falling and prior fracture are risk factors for (future) fracturing[12] has prompted an increased interest in fracture prevention[13,14]. It became clear that there was a need for further evaluating the role of fear of falling as a predisposing factor for fracture risk.

Balance confidence is often used as a measure of fear of falling, and reflects a person's confidence in maintaining balance in different daily life situations[15]. The Activities-specific Balance Confidence Scale (ABC16) was developed to assess an individual's perception of balance confidence, and has been validated in the general population[15] as well as in clinical populations such as post stroke patients and lower limb amputees[16,17]. Most of these studies, however, were performed in small to moderate samples (see table 1), and so far no study has evaluated the psychometric properties of the ABC16 in a population suffering from low-energy fractures.

Patients with low-energy fractures resulting from low trauma events (such as falling) are at high risk for future fractures[12]. Assessment of the psychometric properties of the ABC16 in such a high risk population is thus important as it will assist in optimizing screening protocols for those at risk for future fractures. Accordingly, the current study set out to examine the structural coherence, internal consistency and construct validity of the ABC16 in a Dutch sample of patients aged 50 years and older at risk for future fractures.

Table 1 *Literature overview of validation studies/studies of measurement properties of the Activities-specific Balance Confidence Scale (ABC16)*[1]

Reference	Population	Psychometric assessment	
		Reliability	Structural analysis
Powell & Myers (1995)	60 seniors ≥65 years	+	-
Myers et al. (1998) *	- 37 seniors ≥65 years - 475 older adults - 63 volunteers - 27 osteoarthritic patients >50 years	-	-
Whitney et al. (1999)	71 outpatients of the Jordan Center for Balance and Hearing Disorders in Pennsylvania	-	-
Parry et al. (2001)	189 patients and visitors of the falls and syncope facility.	+	-
Jarlsäter & Mattson (2003)	15 patients from a dizziness and balance outpatient clinic in Sweden	+	-
Miller et al. (2003)	329 participants with a lower-limb amputation	+	-
Hotchkiss et al. (2004)	118 individuals ≥60 years	+	-
Botner et al. (2005)	77 1-year post stroke patients	+	+
Van Heuvelen et al. (2005)	256 participants ≥65 years	+	+
Holbein-Jenny et al. (2005) *	26 elderly residents of a personal care home	+	-
Hsu & Miller (2006)	71 solely Chinese speaking and 38 bilingual participants drawn from the Chinese immigrant population in Vancouver, Canada	+	-
Peretz et al. (2006)	70 higher level gait disorder patients, 19 parkinsons disease patients and 68 healthy controls.	+	-
Salbach et al. (2006)	86 post stroke patients	+	-
Cattaneo et al. (2007)	25 multiple sclerosis patients	+	-
Filiatrault et al. (2007) **	197 seniors	+	-
Mak et al. (2007)	100 cantonese speaking participants, recruited from community-based elderly centers	+	+
Schot et al. (2008)	113 older German adults	+	-
Talley et al. (2008)	272 women ≥70 years	+	-
Huang et al. (2009)	168 community-dwelling older adults ≥60 years	+	-
Arnadottir et al. (2010)	183 icelanders ≥65 years	+	+
Karapolat et al. (2010)	33 patients with unilateral peripheral vestibular disease	+	-
Lohnes et al. (2010)***	98 patients with idiopathic Parkinson	+	-

[1] See Appendix B for reference list

* Discriminative and evaluative properties of the ABC16 are discussed

** Simplified version of the ABC16

*** Shortened versions of the ABC16

METHODS

Participants and study design

Participants were recruited consecutively from a sample of 1339 patients who visited the fracture and osteoporosis outpatient clinics in the city of Eindhoven (the Netherlands) between October 2006 and July 2008, were aged 50 years and older, and had a low-energy fracture in the previous six months. Of all patients approached, 738 showed interest in participating. Participants with insufficient knowledge of the Dutch language (n = 6), cognitive disabilities (*i.e.*, pre-dementia, n = 12) or a history of fracture more than six months ago (n = 35) were not eligible. Ultimately, 534 participants gave written consent to participate. Subsequently, questionnaire packages were mailed out to these participants. Since 34 subjects did not return their questionnaires, and 40 had missing data (> 4 items on the ABC16), the final analyses refer to 460 participants (see table 2). The majority of the sample (n = 380; 83%) was female, with a mean age of participants overall of 66 years (SD = 8.7, range 50-84). There were 25 individuals with a history of multiple fractures. The demographic characteristics, including fracture data of the 460 participating patients were similar to those of the (n = 879) candidate patients who did not participate (data not shown). The study was approved by the medical ethical committee of the Máxima Medical Centre Veldhoven, the Netherlands.

Table 2 *Participant characteristics*

Characteristics	Whole sample N=460	
	n (%)	Mean (SD[1])
Demographic characteristics		
Women	380 (83)	
Age (range 50-84)		65.5 (8.7)
Marital status		
Married/living together	339 (74)	
Single/divorced/widowed	121 (26)	
Education level		
Low	238 (52)	
Moderate	168 (37)	
High	54 (12)	
Monthly income		
<$ 1300	131 (28)	
$1300-$4000	298 (65)	
>$4000	31 (7)	
Fracture characteristics		
Type of fracture according to center[2]		
Hip	39 (8)	
Major	90 (20)	
Minor	241 (52)	
Fingers/toes	90 (20)	
Time since fracture in months		3.0 (1.4)
Use of mobility aid	56 (12)	
≥1 falls in previous 12 months	357 (78)	
Scores on self-rating scales		
ABC16[1] (range 0-100, median 86)		80.2 (20.7)
SF36 GHP[1] (range 0-100, median 70)		66.3 (18.9)
EDS[1] (range 0-30, median 4)		5.5 (5.0)
SCL90[1] anxiety (range 10-50, median 11)		13.0 (3.9)

[1] ABC16=Activities-specific Balance Confidence Scale; EDS=Edinburgh Depression Scale; SCL90=Symptom Checklist 90; SD=Standard Deviation; SF36 GHP=SF36 Health Survey General Health Perceptions Scale

[2] Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007; 297: 387-94.

Data collection

Participant characteristics

Participant characteristics (gender, age, marital status, education level, monthly income, use of mobility aid, one or more falls in the previous 12 months) were measured with a custom-made list of questions. Information on fracture type was provided by the fracture and osteoporosis outpatient clinic, and was classified according to Center *et al.* into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and proximal humerus), minor fractures (all remaining osteoporotic fractures, excluded fingers and toes), and finger and toe fractures[18].

Balance Confidence

The Activities-specific Balance Confidence Scale (ABC16) is a 16-item self-report questionnaire which measures an individual's perception of balance confidence[15]. Participants are asked to indicate their confidence about not falling during a number of specific ambulatory activities (*e.g.* walking around the house, climbing the stairs) on a scale ranging from 0% (no confidence at all) to 100% (total confidence). The overall mean balance confidence score is derived by dividing the summed item score by sixteen (range 0 - 100), with higher scores representing better balance confidence. When ≤ 4 item scores are missing, a total confidence score is calculated by dividing the summed score by the remaining number of answered items[19].

Other Assessments

Health-related Quality of Life

The SF36 Health Survey (SF36) is a 36-item generic questionnaire of perceived health status[20]. The SF36 comprises eight scales, of which only the general health perception scale (5 items) was administered to measure health-related quality of life. Higher scores represent better quality of life. The Dutch version of the SF36 has shown to be a reliable and valid instrument for use in the general population and in patients with chronic disease[21].

Depression

The Edinburgh Depression Scale (EDS) is a 10-item rating scale, typically self-administered, and requiring about five minutes to complete. The EDS evolved from the Edinburgh Postnatal Depression Scale (EPDS), which was originally developed to assess postnatal depression[22]. The Dutch version of the EPDS has been validated, showing appropriate psychometric characteristics[23]. The EPDS was later validated in a group of non-child bearing mothers, and middle aged women as well as subjects over 55 years (men and women) of age which resulted in a new name: the Edinburgh Depression Scale (EDS)[24-26]. The internal consistency of the EDS is good, while its specificity and positive predictive value are considered appropriate[22-26]. The EDS has a maximum score of 30, with a score above 11 as a cut-off to define depression.

Anxiety

The Symptom Checklist 90 (SCL90) is a 90-item self-report scale designed to measure somatic symptoms and psychopathologic features over a seven day period[27]. The SCL90 consists of eight subscales of which the 10-item anxiety subscale (range 10-50) was administered in this study. Items are scored on a five-point Likert scale (1-5), with higher scores indicating higher anxiety levels. The SCL90 and its subscales have been extensively validated[27,28].

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0. To identify the structural coherence of the ABC16 explorative principle component analysis was performed including all 460 cases. Component loadings less than 0.35 were omitted. Internal consistency was calculated using Cronbach's alpha. Construct validity was determined using Pearson correlations between the ABC16 and the general health perception scale of the SF36, the EDS, and the SCL90 anxiety scale.

RESULTS

All items of the ABC16 were found to intercorrelate (> 0.3), the Kaiser-Meyer-Oklin value was greater than 0.6 (*i.e.*, 0.94) and the Bartlett's test of sphericity was significant ($p < 0.001$). Using Kaiser's criterion, the unrotated principle components analysis showed two eigenvalues exceeding 1.0 (*i.e.* 9.48 and 1.22), suggesting a two component solution. The first component explained 59% of the variance, and the second 8%. Because Cattell's scree test clearly suggested a one component solution, and the second component only contributed 8% to the total explained variance, a one component model was chosen. As can be seen in table 3, all loadings were ≥ 0.67.

The Cronbach's alpha of the ABC16 was 0.95. All items were found to measure the same construct, since item-total correlations ranged between 0.65 and 0.81.

In table 4 the correlations between fear of falling, quality of life, depressive symptoms and anxiety are shown. There were 65 participants (14%) who suffered from depression according to the EDS (cut off > 11). Five were male (6%) and 60 were female (16%). The mean score on the ABC16 was 63 in the depressed group, compared to 83 in the non-depressed group ($t = 5.67$, $p < 0.001$).

Table 3 *Factor loadings of the unrotated principle component analysis of the ABC16*

Item content	Component	
	1	2
Walking in a crowd and get bumped	.84	
Walking in a crowded mall	.83	
To sweep the floor	.81	
Reaching while on tiptoes	.81	
Walking up and down the stairs	.80	
Standing on a stepladder to reach	.80	
Walking in the dark	.77	
To pick up something from the floor	.77	
Riding the escalator without holding the handrail	.77	.46
Riding the escalator while holding the handrail	.76	
Cycling on a small cycle path	.76	
Reaching at eye level	.75	-.37
Getting in and out of a car	.73	
Walking outside during the day	.72	
Walking inside the house	.70	
Walking on icy sidewalks	.67	.54

Table 4 *Correlations between the ABC16, quality of life, depression and anxiety*

	ABC16[1]	SF36 GHP[1]	EDS[1]	SCL90 Anxiety[1]
ABC16[1]	1	.46*	-.43*	-.37*
SF36 GHP[1]	.46*	1	-.45*	-.40*
EDS[1]	-.43*	-.45*	1	.70*
SCL90 Anxiety[1]	-.37*	-.40*	.70*	1

* p<.001

[1] ABC16=Activities-specific Balance Confidence Scale; EDS=Edinburgh Depression Scale; SCL90=Symptom Checklist 90; SF36 GHP=SF36 Health Survey General Health Perceptions Scale

Correlations between the ABC16 and anxiety, quality of life and depression were all significant (*p's* < 0.001) and in the expected directions, with a range between 0.37 and 0.46. Finally, the EDS was significantly correlated with the anxiety subscale of the SCL90 (r = 0.70).

DISCUSSION

To our knowledge this is the first study in which the measurement properties of the ABC16 in patients with a low-energy fracture - a population at risk for subsequent fractures[12] - were investigated. The evaluation of the structural coherence of the ABC16 using principal component analysis resulted in a one component solution. Both the internal consistency and construct validity of the ABC16 were found to be appropriate.

Previous research on the ABC16 showed conflicting results regarding its structural coherence. While Mak *et al.*[29] found a straightforward one component solution, Van Heuvelen *et al.*[30], in first instance, suggested a two component solution. However, the latter study nevertheless opted for a one component structure because of the minimum contribution of the second component to the explained variance. Also Botner *et al.*[16] obtained a two component solution: component one included low risk activities with scores > 70, component two included high risk activities with scores < 70.

In the current study the results of a principal component analysis also showed a two component solution, with two eigenvalues exceeding 1. The second component, however, only added 8% to the total explained variance. Our results, thus, converge with those by Mak *et al.*[29] and van Heuvelen *et al.*[30], supporting the notion that the ABC16 can be best used as a one component balance confidence scale.

The internal consistency of the ABC16 was found to be very good ($\alpha = 0.95$). This result concurs with results from several other studies, including the original validation study of the ABC16[15,16,30,31]. Furthermore, also the obtained high item-total correlations underline the fact that the ABC16 items measure the same construct.

The construct validity of the ABC16 was good as indicated by its highly significant correlations with the EDS, the SCL90 anxiety subscale and the SF36 quality of life subscale. The fact that these scales were moderately correlated with the ABC16 (r 0.37-0.46) suggests that balance confidence as measured by the ABC16 is related to, but not identical with depression and anxiety. Recently a significant association between depression and fractures has been reported[32]. Based on the findings of the current study, this association may partially be explained by decreased balance confidence.

Several limitations to the current study need to be acknowledged. Firstly, generalizability of the current findings to the general population is limited. We included only patients aged 50 years and older suffering from a low-energy fracture, and 83% of the sample consisted of women. Secondly, test-retest reliability to confirm the stability of the ABC16 was not performed. Finally, the concurrent validity of the ABC16 was not evaluated with questionnaires measuring the same balance confidence construct. Instead, construct validity was verified using concepts such as depression, anxiety and quality of life who in previous research have been found to be related with balance confidence[5-7].

In conclusion, the ABC16 was found to have good measurement properties. It constitutes a proper tool for measuring balance confidence, which, in turn, signifies fear of falling. Fear of falling is highly prevalent among middle-aged and older persons and heightens the risk of actual falling which, in turn, elevates the risk for fractures. Fracture prevention programs should thus focus on patients with lack of balance confidence who are afraid of falling. We propose to use the ABC16 as a screening instrument in populations at risk for subsequent fractures.

ACKNOWLEDGEMENTS

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APPENDIX A

Dutch version of the ABC16

Deze vragen gaan over angst om te vallen. Wilt u hieronder aangeven hoeveel vertrouwen u in u zelf hebt dat u NIET zult vallen, in de volgende situaties?

0% = totaal geen vertrouwen en 100% = volledig vertrouwen

1. In huis rondlopen _____%
2. Trappen op en aflopen _____%
3. Iets oprapen van de vloer _____%
4. Op ooghoogte reiken _____%
5. Op de tenen staand reiken _____%
6. Op de keukentrap staand reiken _____%
7. De vloer aanvegen _____%
8. Buiten overdag een blokje omlopen _____%
9. In en uit de auto stappen _____%
10. In het donker lopen _____%
11. Fietsen op 'n smal fietspad _____%
12. In een drukke winkelstraat lopen _____%
13. Lopen in een drukke menigte en aangestoten worden _____%
14. Met de roltrap gaan met vasthouden leuning _____%
15. Met de roltrap gaan zonder vasthouden leuning _____%
16. Lopen op een trottoir met ijzel _____%

APPENDIX B

Reference list table 1

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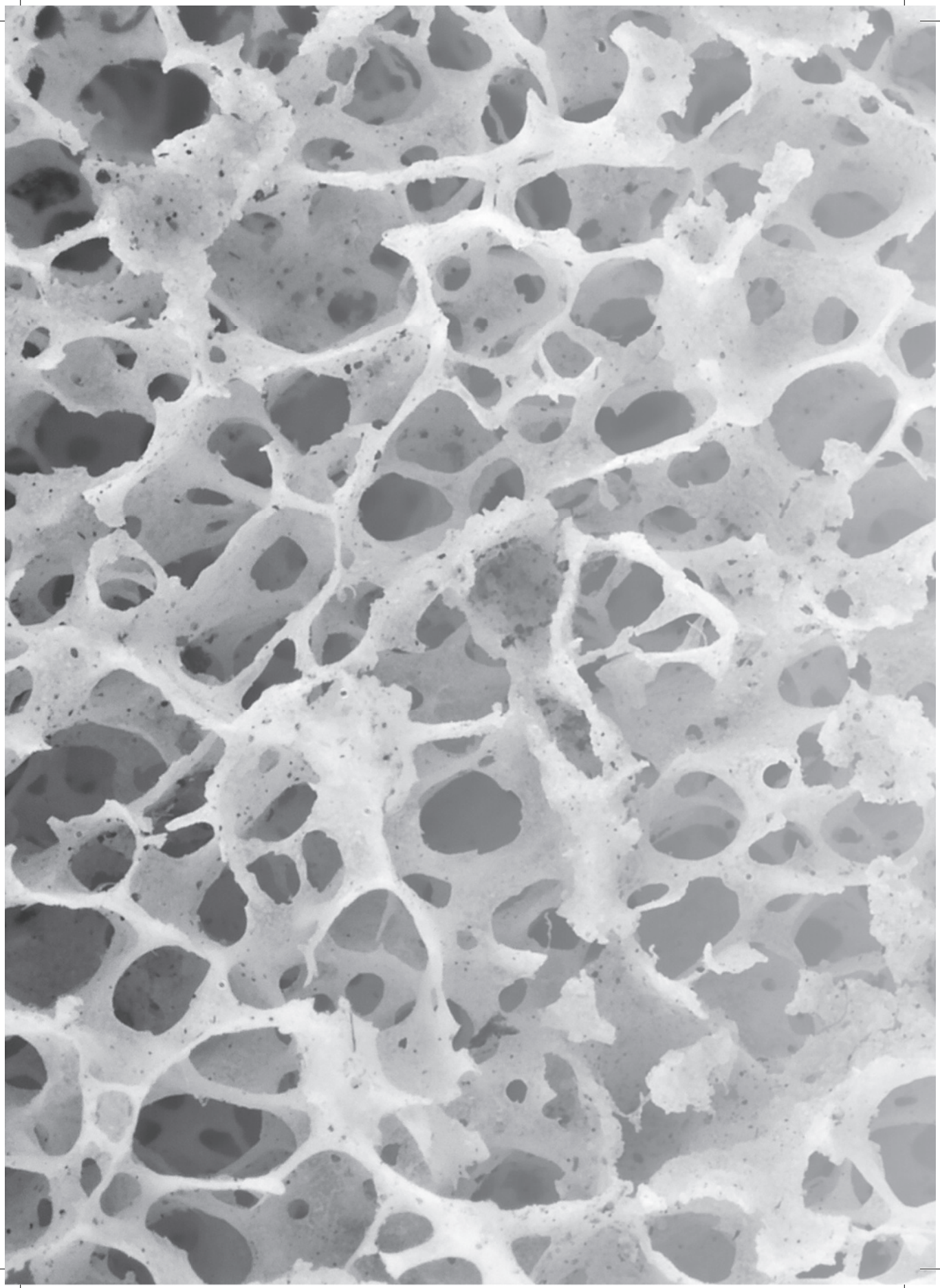

Chapter 4

Depression is common after low-energy fracture in women aged 50 years and older with low bone mineral density

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Submitted to Psychological Medicine

ABSTRACT

Background: Depression and osteoporosis are common in postmenopausal women. Osteoporosis is a major risk factor for fractures. The morbidity of fractures might trigger depression to occur in vulnerable women.

Aim: The current study investigated the occurrence of a major depressive episode during 12 months follow-up in women with a recent low-energy fracture.

Methods: 149 women aged 50 years and older with decreased bone mineral density were followed 12 months after suffering from a low-energy fracture. At baseline the lifetime prevalence and one-month prevalence of a major depressive episode were assessed using the composite international diagnostic interview (CIDI). At 12 months follow-up, the prevalence and incidence of a major depressive episode was assessed with the CIDI.

Results: The lifetime prevalence of depression at baseline was 34% with a one-month prevalence of 12%. The 12-month period prevalence was 11% (n = 17). The 12-month incidence of depression was 8% (n = 12) of whom 9 reported a previous episode earlier in life. The relative risk to develop a new episode of depression after a low-energy fracture in women with a lifetime history of depression was 5.9 (95% CI: 1.5 – 23).

In women of the general population of similar age, a one-year incidence of depression up to 2% has been reported.

Conclusions: Compared to figures of the general population, depression is very common in women over 50 years after a low-energy fracture. Because depression is a major cause of delayed recovery after fracture, clinicians should carefully look at depression after a fracture.

Keywords: depression; incidence; women; low-energy fracture

INTRODUCTION

Osteoporosis is a common disease among the elderly and has a major impact on general health and quality of life. According to the World Health Organization, osteoporosis is defined as a T-score of ≤ -2.5 standard deviation (SD) compared to the normal mean value of bone mineral density (BMD) in young adults[1]. The clinical significance of osteoporosis lies in the associated high risk of fractures. In 2000, 56 million people worldwide suffered from a low-energy fracture[2]. Disability is greatest in patients with hip and lumbar vertebral fractures. Nevertheless, substantial disability has also been reported in patients with other types of fractures[3]. Osteoporosis is a chronic condition and once revealed – as with other chronic medical conditions – could be a risk factor for developing a major depressive episode (MD). From a conceptual point of view, it has been argued that the occurrence of a chronic medical condition (and its related disabilities) could be regarded as a major life event which will trigger – in general or in subjects prone to depression – the development of MD. For example, MD has been reported to occur in 7.9% of patients with congestive heart failure and in 17% of patients with end-stage renal disease[4]. These figures are substantially higher than the 2% in the general elderly population[5]. One study reported that one of every seven patients with a hip fracture developed MD[6]. Apart from the high numbers of MD in chronic medical conditions, the impact of depression on quality of life could be substantial. In a study on older people living independently, it was shown that depressive symptoms delayed recovery in patients who sustained a hip fracture[7,8].

It is obvious that these findings support current clinical advice that, in order to prevent depression in patients suffering from a chronic medical condition, health care professionals should also focus attention on patient mood state, rather than strictly concentrating on the physical disabilities related to the chronic condition. One prospective study showed that, in general, elderly patients with a positive mood state showed better functional recovery after hip fracture over a two-year period[9].

From a biological point of view, several studies have suggested an association between depression, increased fracture risk, and low BMD[10]. Hyperactivity of the hypothalamic pituitary-adrenal (HPA) axis and resulting hypercortisolism are believed to explain this association. From a behavioural perspective, it has been suggested that poor lifestyle, including physical inactivity, nutritional deficiency, excessive alcohol use and smoking (which are all common in patients suffering from depression), may negatively affect bone strength and, therefore, increase the risk of falls and fractures[10]. Moreover, the association between osteoporosis, fractures and depression could be mediated by the use of psychotropic drugs[11].

Finally, from a scientific point of view, observational research of the occurrence of MD after low-energy fractures is important for gaining more insight into explanatory mechanisms. In comparison, for example, with research into the occurrence of postpartum depression, it could be queried why some patients develop MD after a low-energy fracture while most others do not. Does depression after a fracture event preferably occur in patients prone to depression? So far, only two studies have investigated whether there is an association between low-energy fracture and subsequent depression[6,12]. However, one of these only assessed depressive symptoms[12], while the other only took hip fractures into account[6]. Neither study looked into a previous history of episodes of depression.

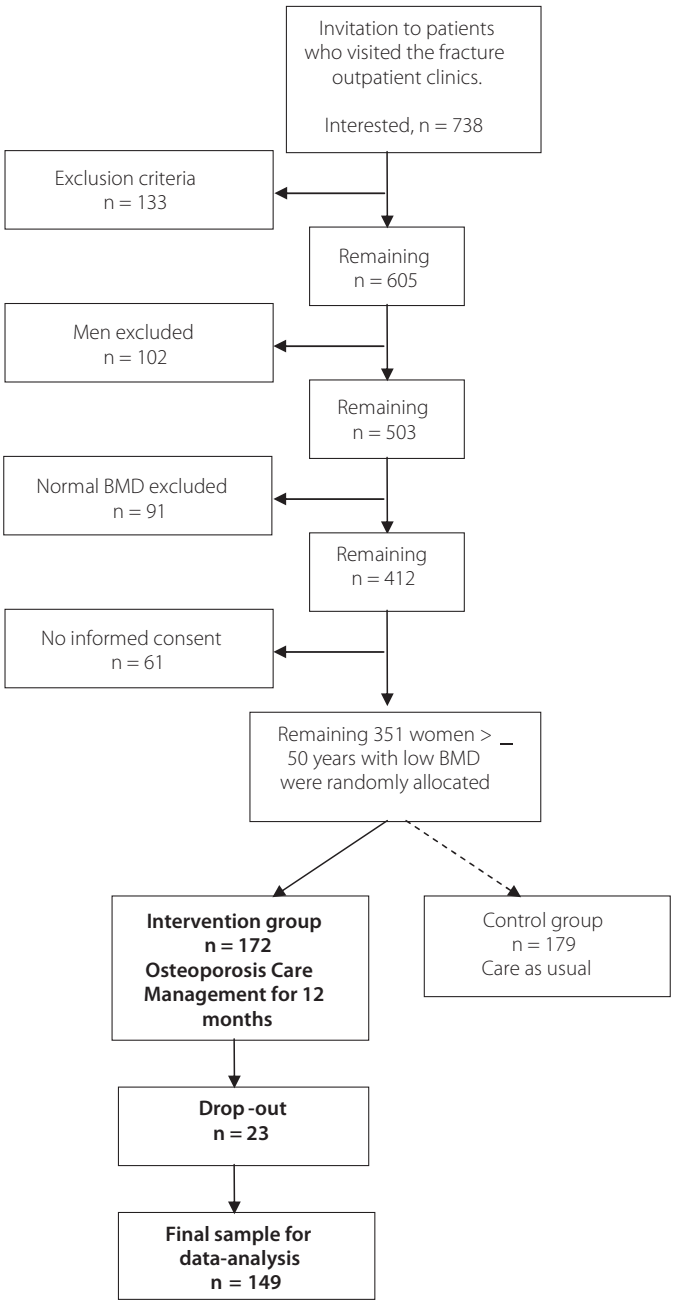
Since women, in general, are more vulnerable to both depression and low-energy fractures[13,14], the current study aimed at investigating the prevalence and incidence of a major episode of depression during 12 months of follow-up in Primary care women aged 50 years and older with low BMD who had suffered a low-energy fracture. We hypothesised that MD occurred much more frequently in these women compared to the general population and that, in particular, women with a previous history of depression would be at risk for developing a further episode of MD after a low-energy fracture.

METHODS

Participants and study design

The current study was part of a larger project on the development of an Osteoporosis Care Management Programme in Primary Care[15]. Between October 2006 and July 2008, Primary care patients who – after a low-energy fracture, defined as resulting from a fall from standing height or lower – visited the fracture and osteoporosis (F&O) outpatient clinics at two teaching hospitals in the south-east of the Netherlands, were informed about the project. The idea of the programme was to investigate the effect of active intervention (in particular regarding the adherence to drug treatment for osteoporosis) and follow-up (especially regarding adherence to lifestyle advice regarding nutrition and daily exercise) of patients with decreased BMD after a low-energy fracture, compared to similar patients who received normal care. The primary outcome measure was a new fracture after follow-up. During the inclusion period, 738 patients who visited the outpatient fracture clinics were interested in participating (figure 1). Of the final 412 women eligible (*i.e.,* those aged 50 years and older with decreased BMD), 351 (85%) ultimately gave their informed written consent to participate, and were subsequently randomly allocated to two groups. The first group (controls, $n = 179$) received care as usual and was referred to a general practitioner (figure 1) with advice for the treatment of decreased BMD. The second group (cases, $n = 172$) was also referred to a general practitioner with similar advice, but in addition, these women received a home visit from a nurse practitioner at baseline and after six and 12 months, as part of an active osteoporosis intervention programme. Moreover, these women were also consulted by telephone after three and nine months of follow-up in order to evaluate whether they were still adhering to drug treatment and to the lifestyle instructions.

In the current study, only data from the second group (cases) were used with regard to baseline and the 12-month follow-up home visit. These 172 women received a set of questionnaires and a structured interview during the home visits (at baseline and after 12 months follow-up) in order to determine the presence of MD. A further 23 women were excluded, due to drop-out before completing the one-year follow-up. Therefore, the data analysis in the current study refers to a final sample of 149 women aged 50 years and older with decreased BMD, who were followed for 12 months after a low-energy fracture. Their characteristics are presented in table 1. The study was approved by the medical ethical committee of the Máxima Medical Centre Veldhoven, the Netherlands.



[a] Insufficient knowledge of the Dutch language n = 6, inadequate cognitive abilities n = 12, a history of fracture > 3 months previously n = 115

Figure 1 *Flowchart of participants included in the current study*

Table 1 *Baseline characteristics of 149 women aged 50 years and older with a history of low-energy fracture and low bone mineral density*

Variable		Study group (n=149)	
		N (%)	*Mean (SD[a])*
Demographic characteristics			
Age			65.8 (8.0)
Marital status	Married/living together	104 (70)	
	Single/divorced/widowed	45 (30)	
Education level	Low	76 (51)	
	Moderate	55 (37)	
	High	18 (12)	
Living independently		105 (70)	
Fracture characteristics			
Type of fracture according to Center[b]	Hip	16 (10)	
	Major	26 (17)	
	Minor	90 (60)	
	Fingers and toes	17 (11)	
Fracture earlier in life		73 (49)	
BMD[a] femoral neck hip			0.65 (0.09)
BMD[a] lumbar spine			0.83 (0.17)
Category of decreased BMD[a]	Osteoporosis	83 (56)	
	Osteopenia	66 (44)	
Psychiatric history			
Major life event during 12-month FU[a]		42 (28)	
Previous history of MD[a]		50 (34)	
Use of anti-depressants		10 (7)	
Lifestyle			
≥3 units of alcohol daily		11 (7)	
Physical inactive		22 (15)	
Current smoking		23 (15)	

[a] BMD=Bone Mineral Density; FU=Follow-up; MD=Major Depression; SD=Standard Deviation

[b] Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007;297:387-94.

Measures

Bone mineral density

BMD was measured using a Hologic W dual energy X-ray absorptiometry system. In accordance with the World Health Organization, osteoporosis was defined as a T-score ≤ -2.5 SD in the spine and/or proximal

femur, osteopenia as a T-score < -1.0 SD and > -2.5 SD, and a normal BMD as a T-score ≥ -1.0. In the current study, only women with decreased BMD were included.

Major depression

At baseline, the lifetime prevalence (women who had experienced an episode of MD at some point before inclusion) and one-month point prevalence (women who had experienced an episode of MD in the one-month period before inclusion) were determined using the Composite International Diagnostic Interview (CIDI version 2.1). The CIDI is a fully structured diagnostic interview which results in the diagnosis presence / absence of lifetime and current diagnoses of MD according to the accepted definitions of DSM-IV[16]. Reliability of the CIDI has been shown to be excellent and the validity has been demonstrated to be adequate [17,18]. At the one-year follow-up, the 12-month period prevalence was assessed. Finally, the 12-month incidence (number of women who were not depressed at baseline and who suffered from one or more episodes of MD during the 12-month follow-up) of MD was assessed.

Statistics

We used descriptive statistics to describe the occurrence of MD after fractures in both groups. To determine differences in BMD of the femoral neck and BMD of the spine between women with and women without lifetime prevalence of MD, and women with or without 12-month incidence of MD, independent samples T-tests were calculated. With respect to differences in diagnosis (osteoporosis versus osteopenia) between women who were or were not classified with a lifetime prevalence of MD, and the women with a presence or absence of 12-month incidence of MD, Chi square tests were calculated. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS) version 18.0.

RESULTS

Table 2 shows the lifetime prevalence, baseline point-prevalence, and 12-month period prevalence. Moreover, the 12-month incidence of a new MD episode during follow-up is also shown. At baseline, 50 women reported a history of MD during their lives (lifetime prevalence: 34%).

At baseline, 18 women were identified with MD in the month prior to inclusion (one-month baseline point prevalence of 12%). Of these, 13 (72%) had been depressed earlier in life. The 12-month period-prevalence of MD at follow-up was 11% (n = 17). Five (29%) of these women had suffered from an episode of MD at baseline and 14 (82%) reported MD earlier in life. By subtracting the five baseline cases from the 12-month period prevalence cases, the 12-month incidence of cases with a new episode of MD was 8% (n = 12). Of these 12 patients with new episodes, nine (75%) reported a previous MD earlier in life. This means that the relative risk (RR) of women aged 50 years and older with a lifetime history of depression for developing a new episode of MD within 12 months after a low-energy fracture is 5.94 (95% CI = 1.53 - 22.98).

Table 2 *Prevalence and incidence of major depression during 12-month follow-up after low-energy fracture in 149 women aged 50 years and older with low BMD*[a]

Occurrence	Definition	N	%
Lifetime history of MD[a]	MD[a] episode at some point during life before inclusion	50	34
1-month point prevalence of MD[a]	MD[a] episode in the one-month period before inclusion	18	12
12-month period prevalence of MD[a]	Patients with (≥ 1) MD[a] episodes during 12-month follow-up irrespective of baseline characteristics	17	11
12-month incidence of MD[a]	New patients with MD[a] episodes (≥ 1) during 12-month follow-up but without MD[a] at baseline	12	8
Healthy women	Women who have never experienced MD[a] in their lifetime or during follow-up	91	61

[a] BMD=Bone Mineral Density; MD=Major Depression

No significant differences were found with respect to BMD of the femoral neck and BMD of the spine between women with and women without a lifetime prevalence of MD or women with or without 12-month incidence of MD. Similar results were found with respect to diagnosis (osteoporosis versus osteopenia).

DISCUSSION

In this study, we found a one-year period prevalence of 11% and a one-year incidence of 8% of MD in women aged 50 years and older with low BMD after a low-energy fracture. Both these prevalence and incidence figures are substantially higher than those reported in the general elderly population, suggesting the major impact of a low-energy fracture. We showed that women with a previous episode of depression had a 5.94 increased risk of further MD after a low-energy fracture.

Literature on the incidence of MD in general is scarce. Wang *et al.*[19] investigated the incidence of MD in a Canadian population and found an overall one-year incidence of 3.3% in women. The one-year incidence decreased with age: the highest being found in 18-25 year-old women (4.3%), while in women aged 46 to 65 years, it was 2.0%. Compared to these results, the one-year incidence of MD in the current study of women with low BMD after a low-energy fracture, is four times higher than that in a similarly-aged group of women from the general population. Another important finding in our study is the high lifetime prevalence of MD (34%). A Dutch study on the prevalence rates of MD in the general population reported a MD lifetime prevalence rate of 20.1% in women[20]. Comparable results were found in a sample of women from the United States: 21.3%[21]. Of the women who developed a depressive episode during follow-up (12-month incidence), 75% had suffered from MD earlier in life. It is well known that women who have earlier suffered from an episode of MD are more prone to developing a further episode, than women who have never suffered from a depressive episode. Previous studies have shown that fractures can have a major impact on daily life[22]. Our findings support the theory that fractures are major life events that can trigger episodes of MD in vulnerable women, *i.e.*, women who have suffered from MD earlier in life.

How can the high incidence of episodes of MD in the low-BMD group be explained? Several studies in women without fractures have suggested that low BMD and depression share a common biological etiological factor[23]. This could explain the high incidence of depression once a fracture has occurred[24]. Other studies suggest that depressed women are at risk for developing future low BMD[25,26], and therefore are at high risk for fractures. It could be hypothesised that this biological explanation is a process that will take several decades to occur. When, in addition to this, these 'biologically prone' women also go through a major life event (a fracture with a major impact on quality of life), the likelihood of developing (another) major depressive episode substantially increases.

Our study is among the first to investigate the incidence of MD after fractures in women with low BMD aged 50 years and older. It is important to point out that we used international diagnostic criteria for defining MD, and that the sample was carefully followed for 12 months, taking into account lifetime history of depression. However, it has several limitations. Firstly, the numbers of participating women was rather low. Secondly, since only women with low BMD were included, our results cannot be generalised to all women aged 50 years and older with low-energy fractures. It is well known that the number of women with low-energy fractures who also have decreased BMD, increases with age[14]. Another limitation is that there could have been a bias in women who decided to participate in the study. Although the study was not explained as a depression follow-up study, depressed women may have been more willing to participate than non-depressed women. It could be suggested that this bias may have resulted in the high lifetime prevalence of MD. However, the association that has been reported in the literature between osteoporosis and depression could also result in the high number: only women with decreased BMD were included. Although we have no details on the psychological characteristics of the non-responders, we do know that there were no significant differences in some important demographic and medical characteristics that are associated with depression (*e.g.*, age, medical status) between our study sample and the total population visiting the F&O clinics. Finally, the occurrence of MD in women with low BMD was not compared to a control group with low-energy fractures but with normal BMD. This was due to the design of the osteoporosis care management programme, in which the effect of drug treatment and active follow-up after low-energy fractures for reducing future fractures, was compared to care-as-usual only in women with decreased levels of BMD. However, despite the above mentioned limitations, the conclusion remains that the one-year incidence of a major depressive episode after a low-energy fracture in women aged 50 years and older is unexpectedly high compared to data from the literature in women of a similar age from the general population.

Our findings show that fractures are associated with a high risk for depression in women who could be biologically prone to depression because of decreased BMD. Therefore, clinicians at fracture outpatient clinics (compared, for example, to clinicians at neurological outpatient clinics seeing patients who recover from CVA) should be aware of this increased risk. Asking about a previous history of MD will detect women at high risk for developing depression. Early intervention strategies (psycho-education, simple cognitive behavioural intervention) in patients at risk will help to prevent depression. It has been shown that depression can have a substantial negative effect on recovery after hip fractures[7,8]. Therefore, assessing the possible existence of depression when recovery is delayed after a fracture could help in

the detection and treatment of depressed patients. Moreover, it has been suggested that depression increases the risk of a subsequent fracture[27], which means that the detection and treatment of depression will help reduce the risk of future fractures. From a conceptual point of view, for future research (using larger samples including women with normal BMD), it might be interesting to investigate whether a specific risk profile can be defined for women who are at risk for developing MD after low-energy fractures.

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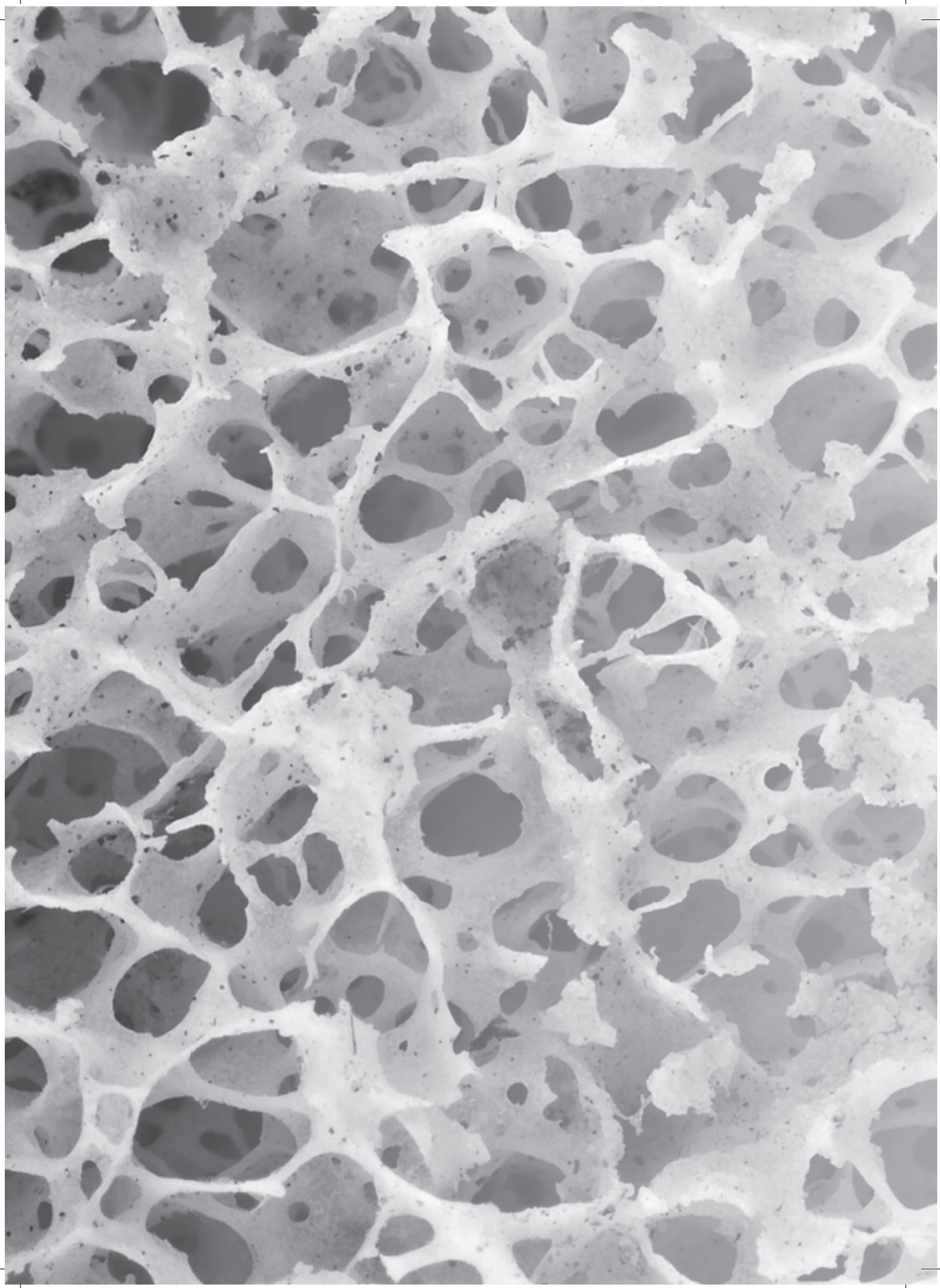

Chapter 5

Depression after low-energy fracture in older women predicts future falls: A prospective study

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ABSTRACT

Background: Falls are one of the main causes of fractures in elderly people. Therefore, in order to prevent fractures, it is important to identify risk factors for falls. Depression has been described as a potential risk factor, though not in patients with a history of fractures. Hence, this study investigated the relationship between depression and the incidence of falls in postmenopausal women with a recent low-energy fracture.

Methods: At baseline, 181 women aged 60 years and older with a recent low-energy fracture were evaluated at the fracture and outpatient clinics of two hospitals. As well as clinical evaluation and bone mineral density tests, the presence of depression (measured using the Edinburgh Depression Scale, EDS, depression cut-off >11) and risk factors for falling were assessed. During two years of follow-up, the incidence of falls was registered annually by means of detailed questionnaires and interviews.

Results: Seventy nine (44%) of the women sustained at least one fall during follow-up. Of these, 28% (n = 22) suffered from depression at baseline compared to 10% (n = 10) of the 102 women who did not sustain a fall during follow-up (X^2 = 8.76, df = 1, p = .003). Multiple logistic regression showed that the presence of depression and co-morbidity at baseline were independently related to falls (OR = 4.14, 95% CI = 1.58-10.82; OR = 2.24, 95% CI = 1.11-4.54, respectively) during follow-up.

Conclusions: The presence of depression in women aged 60 years and older with recent low-energy fractures is an important risk factor for future falls. We propose that clinicians treating patients with recent low-energy fractures should anticipate not only on skeletal-related risk factors for fractures, but also on fall-related risk factors including depression.

Keywords: falls; fractures; women; depression

BACKGROUND

Falls are a major problem in older adults. The incidence increases with age and is higher in women than in men[1,2]. Furthermore, falls are among the main causes of diminished functioning and hospitalisation[3,4]. In 2002, it was estimated that, worldwide, 391,000 people of all ages died of injury-related falls in that year[5]. The costs of non-fatal fall injuries among adults over 64 years of age in the US were estimated at $19 billion in 2000[6].

Up to 70% of low-energy fractures are caused by falls[7,8]. Furthermore, it has been shown that 19% of women with a recent low-energy fracture reported another fall within three months of that fracture[9]. Falls are a strong and independent risk factor for fractures in elderly people[10]. Therefore, after age and bone mineral density (BMD), the number of falls during the past 12 months was included in the recently developed Garvan nomogram that can be used for the calculation of absolute five- and 10-year fracture risk[11,12]. For the prevention of fractures, attention should not only be focussed on the prevention and treatment of low BMD, but also on the prevention of falls.

Several risk factors for falls in older people have been studied. In a recent systematic review, a total of 31 risk factors were distinguished, assessed by at least five studies[1]. Of these, age, female sex, a history of falls, co-morbidity and the use of medication were among the factors most frequently studied, and which had the greatest impact on future falls. Moreover, depression was found to have a negative effect on falls[1].

Depression (high depressive symptom scores as well as syndromic depression) has been described as a potential risk factor for falls in various samples and settings[13-16]. The prevalence of high depressive symptom scores in elderly Dutch women has been estimated to be 17%[17]. In Dutch Primary care, 19% of women aged over 55 years suffer from high depressive symptomatology[18]. Furthermore, it has been shown that depressed patients suffer from poorer recovery after fracture[19,20].

To the best of our knowledge, the relationship between depression and falls in patients with a history of recent low-energy fracture has not yet been studied. Therefore, the current study investigated the occurrence of depression and falls during a two-year follow-up period in postmenopausal women with a recent low-energy fracture.

METHODS

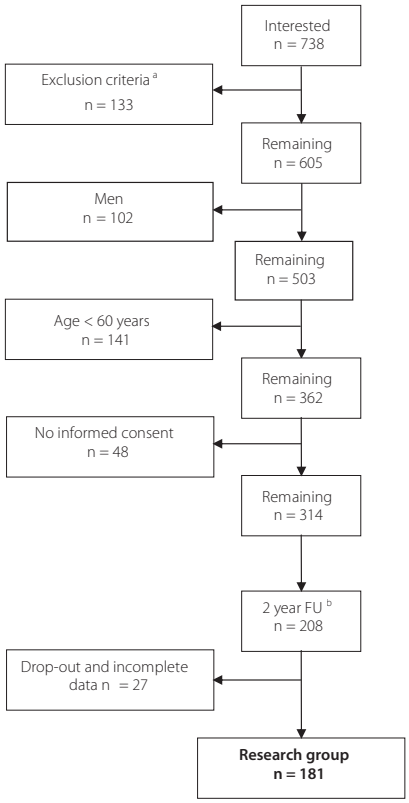
Subjects

The current study was part of a larger project on the development of an osteoporosis care management programme in Primary care[21]. Between October 2006 and July 2008, Primary care patients who visited the fracture and osteoporosis (F&O) outpatient clinics of two hospitals in the south-east of the Netherlands after low-energy fractures (defined as resulting from a fall from standing height or lower), were informed about the project. During the period of inclusion, 738 patients aged 50 years and older who visited the F&O outpatient clinics, were interested in participating (figure 1). After primary fracture care, all patients were invited to undergo BMD measurement and further clinical evaluation by a specialised nurse.

Patients with insufficient knowledge of the Dutch language (n = 6), inadequate cognitive abilities (*i.e.*,

pre-dementia, *n* = 12), or a fracture that had occurred more than three months previously (*n* = 115), were excluded for the current study. Moreover, all men as well as women younger than 60 years of age were also excluded. A total of 362 women were eligible for participation. Ultimately, 314 women (87%) provided written informed consent and 208 completed the two-year follow-up (figure 1).

At baseline, as well as regular F&O assessment, all the patients completed a set of standardised questionnaires for the assessment of depressive symptoms and the presence of risk factors for falling. During follow-up, the incidence of falling was registered annually by means of detailed questionnaires and interviews. Since 27 of the women returned incomplete questionnaires, the final sample for data analysis includes 181 women. All women were advised to use adequate calcium and vitamin D supplementation. Women with osteoporosis were referred to their general practitioner for treatment with anti-osteoporosis medication. The study was approved by the medical ethical committee of the Máxima Medical Centre Veldhoven, the Netherlands, and was carried out in accordance with the Declaration of Helsinki.



[a] Insufficient knowledge of the Dutch language n = 6, inadequate cognitive abilities n = 12, history of fracture > 3 months earlier n = 115

[b] FU=Follow-up

Figure 1 *Flowchart of participants included in the current two-year follow-up study*

Measurements

Demographic and fracture characteristics

Demographic characteristics (age, marital status and education level) were collected using self-report forms (table 1). The demographic characteristics of the women participating in this study were similar to those of the total female population visiting the F&O clinics (data not shown). Information regarding fracture type was provided by the F&O clinics, and was classified according to Center *et al.*[22] into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and proximal humerus), minor fractures (all remaining osteoporotic fractures, excluded fingers and toes), and finger and toe fractures.

Table 1 *Baseline characteristics of 181 women with a recent fracture who did or did not sustain a fall during the two-year follow-up period*

Variable		Did not fall *n* = 102 (%)	Fell *n* = 79 (%)
Demographic characteristics			
Age (mean, SD)*		**67.98 (5.73)**	**70.05 (6.70)**
Marital status	Married/living together	70 (69)	48 (61)
	Single/divorced/widowed	32 (31)	31 (39)
Education	Low	59 (58)	40 (51)
	Moderate	37 (36)	33 (42)
	High	6 (6)	6 (8)
BMD measurements			
BMD Femoral neck hip (mean, SD)		0.68 (0.11)	0.66 (0.11)
BMD Lumbar spine (mean, SD)		0.87 (0.15)	0.84 (0.23)
WHO classification	Osteoporosis	48 (47)	42 (53)
	Osteopenia	32 (31)	26 (33)
	Normal BMD	22 (22)	11 (14)
Type of fracture according to Center[a]	Hip	11 (11)	8 (10)
	Major	24 (24)	15 (19)
	Minor	55 (54)	43 (54)
	Fingers/toes	12 (12)	13 (16)

* $p<.05$

[a] Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007;297:387-394.

Bone mineral density

BMD was measured using a Hologic W Dual energy X-ray Absorptiometry (DXA) system. In accordance with the World Health Organization (WHO) classification, osteoporosis was defined as a T-score ≤ -2.5

SD in the spine and/or femoral neck and/or total hip, osteopenia as a T-score < -1.0 and > -2.5 SD, and normal BMD as a T-score ≥ - 1.0[23].

Risk factors for falling

Risk factors for falling were determined at baseline in accordance with the Dutch guidelines 'Prevention of fall incidents in the elderly'[24,25]. These guidelines were developed in 2004 by the Dutch Institute for Healthcare Improvement[24,25]. The following characteristics were assessed at baseline: age, living alone, ≥1 falls during the 12 months prior to inclusion, use of a walking aid, use of anti-depressants, use of sedatives, use of antihypertensives, ≥2 units of daily alcohol consumption and physical inactivity. The existence of co-morbidity (history of stroke, urinary incontinence, osteoarthritis, rheumatic disease, diabetes and Parkinson's disease) was checked by the specialised nurse, based on the patients' medical records and information from the treating physicians. An overview of the fall-related risk factors is presented in table 2 for women who did or did not sustain a fall during the follow-up period.

Table 2 *The prevalence of fall-related risk factors at baseline in 181 women with a recent fracture who did or did not sustain a fall during the two-year follow-up period*

Variable	Did not fall *n* = 102 (%)	Fell *n* = 79 (%)
Living alone	31 (30)	29 (37)
≥1 fall during 12 months prior to inclusion	77 (75)	66 (84)
Use of walking aid	16 (16)	12 (15)
Comorbidity[a]*	**47 (46)**	**55 (70)**
Use of anti-depressants	3 (3)	5 (6)
Use of sedatives	8 (8)	14 (18)
Use of antihypertensives	35 (34)	25 (32)
≥2 units of daily alcohol consumption	22 (22)	19 (24)
Physical inactivity	14 (14)	16 (20)
Depression according to EDS[b]*	**10 (10)**	**22 (28)**

* $p<.05$

[a] history of stroke, urinary incontinence, osteoarthritis, rheumatic disease, diabetes and Parkinson's disease

[b] score >11

Depressive symptoms

The Edinburgh Depression Scale (EDS)[26] was used to assess depressive symptoms at baseline. The EDS is a 10-item self-rating scale performed over a seven-day period with a four-point scale ranging from 0 to 3 (range 0-30). It was originally designed as the Edinburgh Postnatal Depression Scale (EPDS) for detecting postnatal depression in postpartum women[26]. The Dutch version of the EPDS has been validated showing appropriate psychometric characteristics[27]. The EPDS was later validated in a group of non-childbearing mothers, and middle-aged women, as well as in subjects aged over 55 years (men

and women), and renamed the Edinburgh Depression Scale (EDS)[28-30]. The internal consistency of the EDS is good and its specificity and positive predictive value are appropriate[26-30]. In the present study, depression was defined as an EDS score >11.

Statistical analyses

In order to determine differences in baseline characteristics, including the presence of depression, between women who did or did not sustain a fall during the follow-up period, independent samples T-test and Chi-square tests were used. Unadjusted ORs ($p < 0.05$, 95% CI) were calculated using single logistic regression analyses, with falls as the dependent variable. Adjusted ORs were calculated using multiple logistic regression analysis, with the occurrence of falls during the two-year follow-up period as the dependent variable, entering all risk factors into the regression analysis. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS) version 18.0.

RESULTS

The mean age of the participating women was 69 years (range, 60-84) and the majority was either married or living together with a partner (65%). During the two-year follow-up period, 44% ($n = 79$) of the women sustained at least one fall; there were 220 incidents of falls in these 79 women (mean = 2.78; SD = 2.58). Women who sustained a fall during follow-up were significantly older than those who did not (t = 2.19, $p = 0.03$; table 1). There was no significant difference in BMD, WHO T-score classification, or type of fracture between the two groups.

Of the 79 women who sustained a fall during follow-up, 57 (72%) fell at least once in the first year, and 43 (54%) fell at least once during the second year. The number of women who sustained a first fall during the first year ($n = 57$) was significantly larger compared to that during the second year ($n = 22$) ($X^2 = 18.72$, df = 1, $p < .001$). However, with regard to the total number of falls ($n = 220$), there was no significant difference between the 116 falls (53%) occurring in the first year of follow-up (57 women) and the 104 (47%) occurring in the second year (43 women). Thirty-nine percent ($n = 31$) of the women who sustained a fall during follow-up fell once, 25% ($n = 20$) fell twice, and 35% fell three or more times ($n = 28$).

Thirty-two women (18%) suffered from depression at baseline (EDS scores > 11). Of the 79 women who sustained a fall during follow-up, 28% ($n = 22$) suffered from depression at baseline, compared to 10% ($n = 10$) of the 102 who did not sustain a fall ($X^2 = 8.76$, df = 1, $p = .003$). Depression at baseline was not related to the number of falls (once or more during the follow-up period) nor to the time of falling (first- and/or second-year, data not shown). The prevalence of co-morbidity at baseline was significantly higher in women who sustained a fall during follow-up compared to those who did not ($X^2 = 9.10$, df = 1, $p = .003$; table 2).

The results of single logistic regression analyses are shown in table 3a. Greater age (OR = 1.06, 95% CI = 1.01-1.11), presence of co-morbidity (OR = 2.68, 95% CI = 1.45-4.97), use of sedatives (OR = 2.53, 95% CI = 1.01-6.38), and depression according to the EDS (OR = 3.55, 95% CI = 1.57-8.04), were found

to be significantly related to future falls. Multiple logistic regression showed that the presence of co-morbidity (OR = 2.24, 95% CI = 1.11-4.54) and depression (OR = 4.14, 95% CI = 1.58-10.82) at baseline were independently related to future falls (table 3b).

Table 3a *Single logistic regression, dependent variable: sustaining future falls during the two-year follow-up period in 181 women with a recent low-energy fracture*

Variable at baseline	OR	95% CI
Age*	**1.06**	**1.01 - 1.11**
BMD femoral neck hip	0.17	0.01 - 2.89
Living alone	1.33	0.71 - 2.48
History of falls during 12 months prior to inclusion	1.65	0.78 - 3.48
Use of walking aid	0.96	0.43 - 2.17
Comorbidity[a]*	**2.68**	**1.45 - 4.97**
Use of anti-depressants	2.23	0.52 - 9.63
Use of sedatives*	**2.53**	**1.01 - 6.38**
Use of antihypertensives	0.89	0.47 - 1.66
≥2 units of daily alcohol consumption	1.15	0.57 - 2.32
Physical inactivity	1.60	0.73 - 3.51
Depression according to EDS[b]*	**3.55**	**1.57 - 8.04**

* $p<.05$
[a] history of stroke, urinary incontinence, osteoarthritis, rheumatic disease, diabetes and Parkinson's disease
[b] score >11

Table 3b *Multiple logistic regression, dependent variable: sustaining future falls during the two-year follow-up period in 181 women with a recent low-energy fracture*

Variable at baseline	Adjusted OR	95% CI
Age	1.03	0.96 - 1.09
BMD femoral neck hip	0.19	0.01 - 6.30
Living alone	1.26	0.61 - 2.61
History of falls during 12 months prior to inclusion	1.70	0.71 - 4.08
Use of walking aid	0.47	0.17 - 1.29
Comorbidity[a]*	**2.24**	**1.11 - 4.54**
Use of anti-depressants	1.61	0.23 - 11.13

Table 3b *(Continued)*

Variable at baseline	Adjusted OR	95% CI
Use of sedatives	2.44	0.81 - 7.34
Use of antihypertensives	1.09	0.53 - 2.22
≥2 units of daily alcohol consumption	1.28	0.58 - 2.83
Physical inactivity	1.47	0.61 - 3.57
Depression according to EDS[b]*	**4.14**	**1.58 - 10.82**

* $p<.05$

[a] history of stroke, urinary incontinence, osteoarthritis, rheumatic disease, diabetes and Parkinson's disease

[b] score >11

DISCUSSION

This study shows that the presence of depression after a recent low-energy fracture was an independent risk factor for future falls during a two-year follow-up period in postmenopausal women (OR = 4.14, 95% CI = 1.58-10.82). Moreover, the existence of co-morbidity increased the risk of falls within two years (OR = 2.24, 95% CI = 1.11-4.54).

Depression at baseline (EDS scores > 11) was present in 18% of the women, which is comparable to other studies carried out in the Netherlands. Beekman *et al.*[17] reported a prevalence of 17% in a general population Dutch women aged over 60 years, while another Dutch Primary care study reported a prevalence of 19%[18].

The one-year incidence of falls among community-dwelling elderly has been estimated at 30%, which is in accordance with our findings (31%)[1]. The number of falls was equally distributed over the two-year follow-up period. However, 72% of the women who sustained a fall during follow-up, fell during the first year of follow-up, while 28% sustained their first fall in the second year. Therefore, the number of falls did not decline over time, but the incidence of women with a new, first fall did. This means that the women who sustained their first fall in the first year of follow-up had a high risk of falling during the second year. It has repeatedly been reported in the literature that a history of a previous fall is a particular risk factor for subsequent falls[2,15,31]. However, in the present study, the history of a fall during the 12 months prior to inclusion did not affect the risk of falling during the two-year follow-up period.

In contrast, falls occurred significantly and independently more often in women who were depressed at baseline compared to non-depressed women. In a large sample of older women from the general population (with no recent history of low-energy fracture), Whooley *et al.*[16] showed that depression and falls were independently related during two years of follow-up (OR 1.4). Stalenhoef *et al.*[15] showed that the risk for falling was about twice as high in depressed Primary care patients (with no history of a recent low-energy fracture) compared to non-depressed subjects.

The presence of co-morbid conditions at baseline (*e.g.*, osteoarthritis, diabetes, Parkinson's disease) was also significantly related to falls during the two-year follow-up. Most of these conditions interfere with normal balance and physical activity and are well known risk factors for falling[1].

Sustaining a fracture can have a major impact on daily life[32], which can result in depression. In turn, depression after a fracture has been shown to be a risk factor for delayed recovery[19,20,33]. Moreover, this study points out that depression is an important risk factor for future falls in women with a recent low-energy fracture, thereby substantially increasing the risk of subsequent fractures. BMD was not related to the incidence of falls. However, it has repeatedly been reported that fractures after falls are particularly common in patients with osteopenia[34,35].

Several limitations of the present study should be mentioned. Firstly, a bias could have occurred due to the high non-response rate. Depressed women may have been more willing to participate in our study than non-depressed women. Although we have no detailed data on the characteristics of the non-responders, we do know that there were no significant differences between the demographic characteristics (which are important general determinants of depression) of our sample and those of the total population that visited the F&O clinics. Moreover, the number of women with depression according to the EDS was similar to that of the general postmenopausal population, again suggesting no bias. Secondly, we did not assess depression at a syndromic level, which would usually be performed during a structural interview. During such an interview, there is also the opportunity to assess lifetime history of depression and/or chronic episodes of depression. It would be interesting to discover whether women with a previous history of depression are particularly at risk for another depressive episode after a low-energy fracture, and hence for the incidence of future falls. Thirdly, we assessed falls annually by means of detailed questionnaires and interviews, as opposed to using a diary. This may have led to an underestimation of the number of falls. A further limitation is that we did not include other known determinants of falls (*e.g.*, vision disabilities, normal daily activities, dizziness).

In regular outpatient F&O clinics, most clinicians concentrate on the presence of skeletal-related risk factors for fractures (osteoporosis, family history of hip fracture, glucocorticoid use) rather than on risk factors associated with future falls. Depression is an important risk factor for future falls and is associated with delayed recovery. Based on the findings from the present study, we propose that clinicians who are treating patients with recent fractures should anticipate on the presence of depression. Further research is needed to evaluate the effect of treatment and the prevention of depression after a recent fracture.

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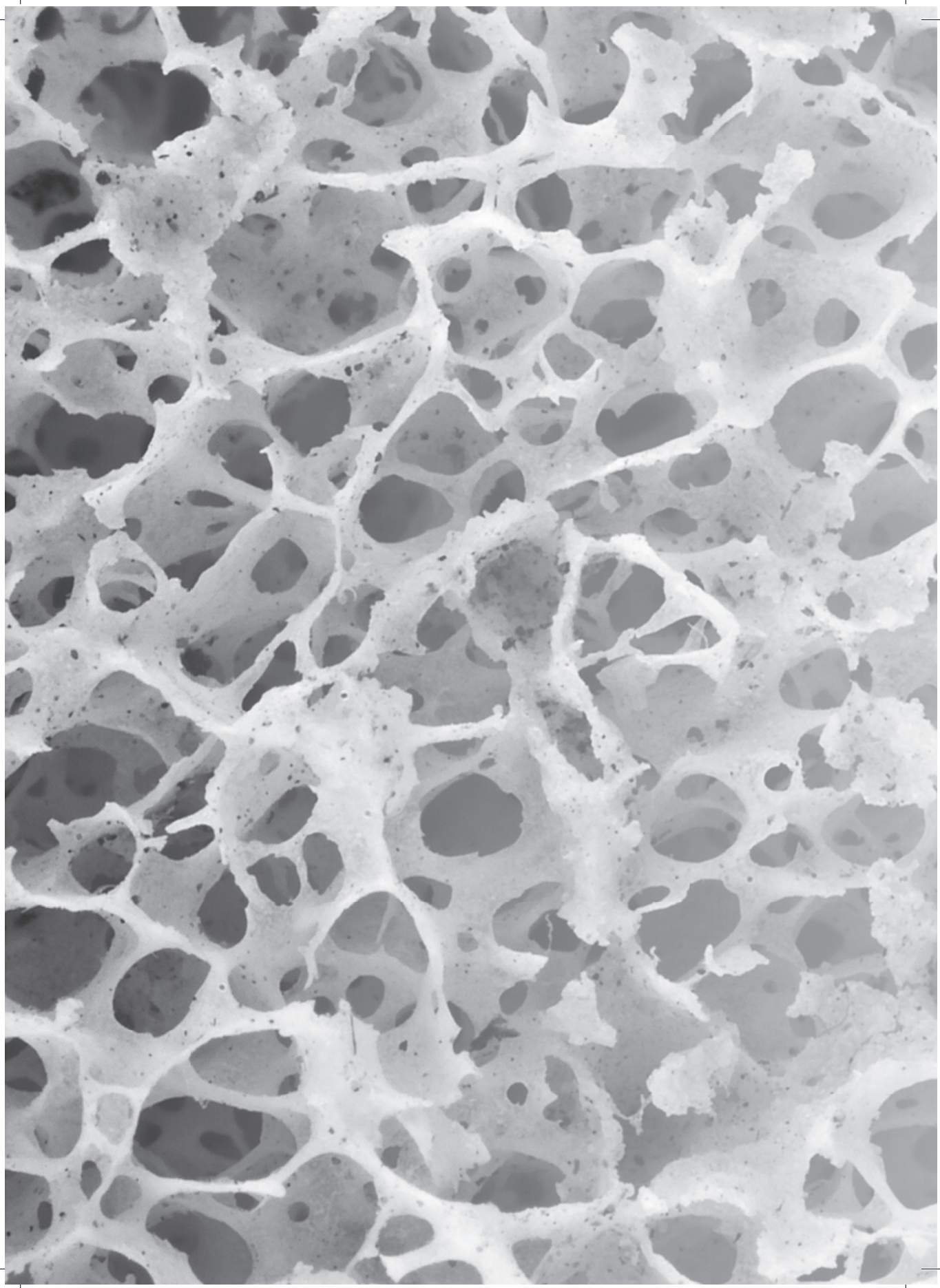

Chapter 6

Use of Garvan and FRAX® in short term fracture risk assessment

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ABSTRACT

Background: This study assessed the applicability of the Garvan nomogram and the FRAX® to predict short term fracture risk in women aged 60 years and older with a recent low-energy fracture.

Methods: 173 women aged 60 years and older, with a recent low-energy fracture, were followed for a period of two years. Clinical risk factors according to Garvan and FRAX® were assessed at baseline. Subsequent fractures were registered yearly.

Results: 13.3% of the women (n = 23) sustained a subsequent fracture (any fracture) and 6.4% (n = 11) a subsequent major osteoporotic (clinical spine, forearm, hip or shoulder) fracture during follow-up. Five- and 10-year fracture risk predictions by Garvan were 19.9% and 36.3% respectively. Ten-year prediction of a major osteoporotic fracture by FRAX® was 12.4%. Women who sustained a subsequent fracture during follow-up had significantly higher five- and 10-year risk scores according to Garvan than women who did not (27.7% versus 18.7%, p = .029; and 46.6% versus 34.8%, p = .020, respectively). No differences were found with respect to FRAX®. The ROC curve showed a significant result for Garvan (AUC = 0.67, 95% CI = 0.55-0.78, p = .011), however it was not possible to determine an optimal cut-off value for both Garvan and FRAX®.

Conclusions: Garvan predicted a significantly higher fracture risk in patients who sustained a subsequent fracture within two years, while FRAX® did not. At an individual level, both fracture risk calculators could not be used to discriminate between those who sustained a subsequent fracture and those who did not.

Keywords: osteoporosis; fracture; FRAX®; Garvan fracture risk calculator; women

INTRODUCTION

Osteoporotic fractures are a major public health problem. In 2000, the number of new osteoporotic fractures worldwide was estimated at 9 million. During the same year, 56 million persons suffered from disability caused by a fracture with a female-to-male ratio of 1.6[1]. These numbers are expected to rise with prolonged life-expectancy and the worldwide ageing of the population. Fractures are found to have a negative impact on health related quality of life, morbidity and mortality in postmenopausal women[2-5]. Furthermore, costs associated with osteoporotic fractures are substantial[6]. Therefore assessment of fracture risk plays a key role in osteoporosis management.

In 2008, the fracture risk assessment tool (FRAX®) was released using an extensive set of clinical risk factors with and without bone mineral density (BMD) for 10-year fracture risk prediction of hip and major osteoporotic (clinical spine, forearm, hip or shoulder) fractures in men and women[7,8]. Recently, the Garvan nomogram was developed which combines BMD or body mass index (BMI) with clinical risk factors (*i.e.* age, prior fracture and history of falls) in order to predict five- and 10-year risks of hip fracture and any osteoporotic fracture in persons aged 60 to 96 years[9,10].

It is known that a prior fracture significantly increases the risk of subsequent fractures at other skeletal sites[11,12]. The majority of subsequent fractures occur within the first five years after the initial fracture[13]. The increased risk of subsequent fracture applied for virtually all types of low-energy fractures and persisted for up to 10 years depending on age and sex[13]. More recently it has been shown that clinical fractures cluster in time from menopause onward, with one out of four subsequent fractures occurring within one year after the first fracture[14]. In a two-year follow-up study, the absolute new fracture risk was 10.8% for any clinical fracture, of which 60% occurred within one year after the initial fracture[15]. Another study reported on the incidence of fractures on the hip, forearm, shoulder and vertebrae. They reported an incidence of an identical fracture of 21% within five years following the initial fracture, with the highest incidence within one year after the initial fracture[16].

Based on the recent findings of increased risk of subsequent fracture after an initial fracture, we aimed to investigate the applicability of the Garvan and FRAX® fracture risk calculators for short term fracture risk assessment in women aged 60 years and older who had recently suffered from a low-energy fracture in a two-year follow-up study.

MATERIALS AND METHODS

Participants and study design

The current study was part of a larger project concerning the development of an Osteoporosis Care Management Programme in Primary care[17]. Between October 2006 and July 2008, Primary care patients who visited the fracture and osteoporosis outpatient clinics, after suffering from a low-energy fracture, were informed about the project. The participating fracture and osteoporosis clinics are situated in the south-east part of the Netherlands. Low-energy trauma is defined as fracture resulting from a fall from standing height or lower. In total, 738 patients aged 50 years and older were interested to participate (figure 1). After primary fracture care, all patients were invited for BMD measurement and further clinical

evaluation by a specialised nurse. All women were advised to use adequate calcium and vitamin D supplementation. Women with osteoporosis were referred to their general practitioner for treatment with anti-osteoporosis medication.

Patients with insufficient knowledge of the Dutch language (n = 6), inadequate cognitive abilities (*i.e.* pre-dementia, n = 12) or a fracture more than three months ago (n = 115) were excluded. Furthermore all men and women younger than 60 years of age were also excluded for the current study. None of the participants exceeded the maximum age of 96 years as applied by Garvan. A total of 362 women were eligible to participate. Ultimately, 314 women gave written informed consent of whom 208 were followed for 24 months.

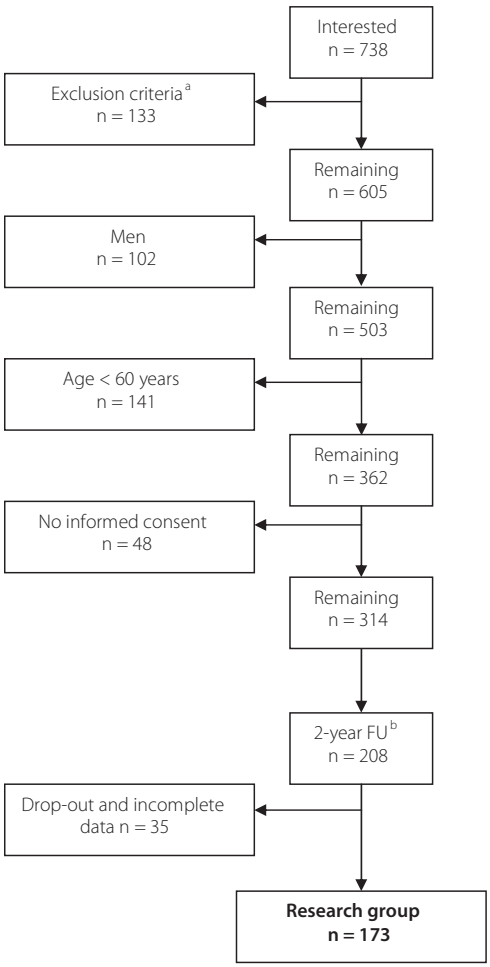
During follow-up, subsequent fractures were registered yearly by detailed questionnaires and interviews. Because of incomplete data in 35 women, the final sample for data analysis includes 173 women of whom the characteristics are shown in table 1. The study was approved by the medical ethical committee of the Máxima Medical Centre Veldhoven, the Netherlands, and was carried out in accordance with the Declaration of Helsinki.

Table 1 *Demographic characteristics for 173 women aged ≥ 60 years*

Variable		Subsequent fracture (n = 23)	No subsequent fracture (n = 150)	*p*
Demographic characteristics				
Age (mean, SD[a])		68.91 (7.47)	68.82 (6.08)	.95
Marital status	Married/living together	12 (52%)	102 (68%)	.21
	Single/divorced/widowed	11 (48%)	48 (32%)	.21
Education	Low	9 (39%)	87 (58%)	.14
	Moderate	12 (52%)	54 (36%)	.21
	High	2 (9%)	9 (6%)	.97
BMD[a] measurements				
WHO[a] classification	Osteoporosis	11 (48%)	74 (49%)	1.00
	Osteopenia	10 (43%)	47 (31%)	.36
	Normal BMD	2 (9%)	29 (19%)	.34
Type of fracture according to center[b]	Hip	5 (22%)	14 (9%)	.16
	Major	2 (9%)	35 (23%)	.19
	Minor	12 (52%)	80 (53%)	1.00
	Fingers/toes	4 (17%)	21 (14%)	.91
Falls during follow-up				
Fell during first year of follow-up		14 (61%)	41 (27%)	.003
Fell during second year of follow-up		6 (26%)	14 (9%)	.04

[a] BMD=Bone Mineral Density; SD=Standard Deviation; WHO=World Health Organization

[b] Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007; 297: 387-394.



[a] Insufficient knowledge of the Dutch language n = 6, inadequate cognitive abilities n = 12, a history of fracture > 3 months ago n = 115

[b] FU=follow-up

Figure 1 *Flowchart of participants included in the current two-year follow-up study*

Data Collection

Bone mineral density

BMD was measured using a Hologic W Dual Energy X-ray Absorptiometry (DXA) system. In accordance with the World Health Organization (WHO) classification, osteoporosis was defined as a T-score ≤ -2.5 SD in the spine and/or proximal femur, osteopenia as a T-score < -1.0 and > -2.5 SD, and normal BMD as a T-score ≥ -1.0[18].

Fracture

Information regarding fracture type at baseline was provided by the fracture and osteoporosis clinics, and was classified according to Center *et al.*[13] into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and proximal humerus), minor fractures (all remaining osteoporotic fractures, excluded fingers and toes) and finger and toe fractures. During follow-up, subsequent fractures were registered yearly by detailed purpose designed questionnaires and interviews. Both fracture at baseline and subsequent fracture were radiographically confirmed.

Garvan and FRAX®

Risk factors according to Garvan and FRAX® were assessed at baseline with standardised questionnaires. In the present study, we used femoral neck BMD and not body weight for the Garvan model. Age and BMD of the femoral neck were used in both Garvan and FRAX® in order to calculate fracture risk[9,10,19-22]. Garvan further incorporates number of fractures since the age of 50 and the number of falls during the past 12 months[9,10]. FRAX® uses height, a previous fracture[23], a family history of hip fracture[24], current smoking[25], use of glucocorticoids (≥ 3 months, dosage ≥ 5 mg prednisolone)[19], rheumatoid arthritis, secondary osteoporosis and a daily intake of ≥ 3 units alcohol[26]. In table 2 the prevalence of risk factors at baseline in the participating women according to Garvan and FRAX® are presented.

Table 2 *Risk factors with respect to the Garvan nomogram and the FRAX® algorithm for 173 women with a prior fracture aged ≥ 60 years*

	Garvan			FRAX®		
Risk factors	Subsequent fracture (n=23)	No subsequent fracture (n=150)	*p*	Subsequent MO[a] fracture (n=11)	No subsequent MO[a] fracture (n=162)	*p*
Both in Garvan and FRAX®						
Age (mean, SD[a])	68.91 (7.47)	68.82 (6.08)	.95	69.18 (6.46)	68.81 (6.12)	.89
Femoral neck BMD[a,b] (mean, SD)	**0.62 (0.11)**	**0.67 (0.11)**	**.03**	0.64 (0.14)	0.67 (0.11)	.55
Weight[b] (mean, SD)	68.57 (12.80)	70.51 (11.25)	.45	72.27 (14.33)	70.12 (11.26)	.55
Garvan						
Number of Fractures > 50 years[c]						
1	12 (52%)	111 (74%)	.06			
2	9 (39%)	35 (23%)	.17			
≥ 3	2 (9%)	4 (3%)	.39			
Number of falls over last 12 months[d]						
0	3 (13%)	34 (23%)	.44			
1	12 (52%)	93 (62%)	.50			
2	4 (17%)	17 (11%)	.63			
≥ 3	**4 (17%)**	**6 (4%)**	**.04**			

Table 2 *(Continued)*

Risk factors	Garvan			FRAX®		
	Subsequent fracture (n=23)	No subsequent fracture (n=150)	*p*	Subsequent MO[a] fracture (n=11)	No subsequent MO[a] fracture (n=162)	*p*
FRAX®						
Height (mean, SD)				161.1 (7.6)	162.9 (6.5)	.39
Previous fracture[e]				11 (100%)	162 (100%)	n.a.
Parent fractured hip				3 (27%)	33 (20%)	.87
Current smoking				1 (9%)	19 (12%)	1.0
Glucocorticoids[f]				1 (9%)	6 (4%)	.93
Rheumatoid arthritis				1 (9%)	15 (9%)	1.0
Secondary osteoporosis[g]				1 (9%)	44 (27%)	.33
Alcohol ≥ 3 units per day				-	9 (6%)	n.a.

[a] BMD=Bone Mineral Density; MO=Major Osteoporotic; SD=Standard Deviation
[b] Either bone mineral density or body weight is used in the Garvan fracture risk calculator.
[c] Excluding fractures caused by major trauma, including fracture at baseline.
[d] Including falls at baseline.
[e] A previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture.
[f] Past or present exposure to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids).
[g] Presence of a disorder strongly associated with osteoporosis, including: Type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, or malabsorption and chronic liver disease.

STATISTICAL METHODS

Fracture probabilities of any fracture according to Garvan and major osteoporotic fracture according to FRAX® were calculated[27,28]. Since the number of subsequent hip fractures in our study was small, we only present the risk for any fracture for calculations of Garvan and the risk for major osteoporotic fractures (clinical spine, forearm, hip or shoulder) for FRAX®. To assess the number and percentage of all, and major osteoporotic fractures in our study during two-year follow-up, the five- and 10-year risk of any fracture according to Garvan and the 10-year risk of a major osteoporotic fracture according to FRAX®, descriptive statistics were used. In order to determine differences in Garvan and FRAX® risk scores between women with and women without a subsequent fracture, independent samples T-tests were calculated.

Next, fracture risk cut-off points for both Garvan and FRAX® were determined based on the 20, 25, 30, 40 and 50 percentile in women with a subsequent fracture in order to assess the usefulness of both models for short term fracture risk prediction. Subsequently ROC curves were assessed in order to determine if an optimal cut-off value is present for determining short term fracture risk with respect to sensitivity and specificity. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (IBM SPSS) version 18.0.

RESULTS

Mean age of the participating women was 69 years (SD = 7.5). In total, 85 women were diagnosed with osteoporosis (49.1%), 57 (32.9%) with osteopenia and 31 (17.9%) had a normal BMD (table 1).

During two-year follow-up, a total of 23 (13.3%) women suffered a subsequent fracture, of which 10 (43.5%) occurred during the first year and 13 (56.5%) during the second year of follow-up. A subsequent major osteoporotic fracture occurred in 11 (6.4%) women during follow-up, of which 8 (72.7%) occurred during the first year and 3 (27.3%) during the second year of follow-up. Women who sustained a subsequent fracture during follow-up had significant lower BMD of the femoral neck at baseline compared to women who did not sustain a subsequent fracture (table 2; t = 2.16, df = 171, p = .032). In addition, women with a subsequent fracture fell significantly more often three or more times during the past 12 months before inclusion (17.4%) compared to women who did not sustain a subsequent fracture during follow-up (4.0%; X^2 = 4.34, df = 1, p = .04). No further significant differences were found between women with and without a subsequent fracture during follow-up (table 2). However, with respect to the number of previous fractures at baseline, a result of clinical significance was found: 48% of the women who sustained a subsequent fracture had ≥ 2 previous fractures compared to 26% of the women who did not (table 2; X^2 = 3.62, df = 1, p = .057).

The mean five- and 10-year risk scores for any fracture according to Garvan were 19.9% (SD = 11.7) and 36.3% (SD = 17.05) respectively. The mean 10-year risk for a major osteoporotic fracture according to FRAX® was 12.4% (SD = 7.9). Women who sustained a subsequent fracture during follow-up had significantly higher five- and 10-year Garvan risk scores at baseline (five- and 10-year risk of 27.70 ± 18.02 and 46.56 ± 21.86 respectively) compared to women who did not suffer a subsequent fracture (mean five- and 10-year risk 18.74 ± 9.94 and 34.78 ± 15.70, respectively; t = -2.33, p = .029 and t = -2.49, p = .020 respectively). No significant differences were found for the 10-year major osteoporotic fracture risk scores using FRAX® between women with (n = 11, mean = 15.25, SD = 12.00) and women without (n = 162, mean = 12.23, SD = 7.51) a subsequent major osteoporotic fracture during two-year follow-up.

In table 3a and 3b, the sensitivity, specificity, positive predictive value and the negative predictive value of various cut-off values based on percentiles of five- and 10-year fracture risk calculations using the Garvan nomogram for women with and without a subsequent fracture during two-year follow-up are presented. As shown, specificity is low, meaning a high percentage of women without a subsequent fracture during follow-up had fracture risk scores above the various fracture risk cut-off values. In table 3c the results with regard to FRAX® are presented. Using FRAX®, results were comparable, however, specificity was lower compared to Garvan.

The ROC curve on any fracture according to Garvan, showed a significant result for both five- and 10-year fracture risk predictions (AUC = 0.67, 95% CI = 0.55-0.78, p = .011; AUC = 0.67, 95% CI = 0.55-0.78, p = .011 respectively). However, it was not possible to determine an optimal cut-off value based on sensitivity and specificity. No significant results were found on the ROC curve of the FRAX® 10-year risk score (AUC = 0.56, 95% CI = 0.37-0.75, p = .524).

Table 3a *Validity of the Garvan model (five year risk of any fracture taking into account BMD[a] and the initial fracture) using different percentile cut-off scores to predict a subsequent fracture in postmenopausal women during two-year follow-up after a low-energy fracture.*

Percentile (cut-off value)	Sensitivity	Specificity	PPV[a]	NPV[a]
20% (13.90)	78	41	17	92
25% (14.20)	74	43	17	91
30% (14.70)	70	45	16	91
40% (19.70)	57	65	20	91
50% (20.50)	48	67	18	89

[a] BMD=Bone Mineral Density; NPV=Negative Predictive Value; PPV=Positive Predictive Value

Table 3b *Validity of the Garvan model (10 year risk of any fracture taking into account BMD[a] and the initial fracture) using different percentile cut-off scores to predict a subsequent fracture in postmenopausal women during two-year follow-up after a low-energy fracture.*

Percentile (cut-off value)	Sensitivity	Specificity	PPV[a]	NPV[a]
20% (27.50)	78	43	17	93
25% (27.90)	74	43	17	92
30% (28.90)	70	48	17	91
40% (37.50)	57	65	20	91
50% (38.80)	48	68	19	89

[a] BMD=Bone Mineral Density; NPV=Negative Predictive Value; PPV=Positive Predictive Value

Table 3c *Validity of the FRAX® model (10 year risk of major osteoporotic fracture taken into account BMD[a] and the initial fracture) using different percentile cut-off scores to predict a subsequent fracture in postmenopausal women during two-year follow-up after a low-energy fracture.*

Percentile (cut-off value)	Sensitivity	Specificity	PPV[a]	NPV[a]
20% (7.20)	73	22	1	92
25% (7.20)	73	22	1	92
30% (10.00)	46	57	7	94
40% (10.00)	46	57	7	94
50% (10.00)	46	57	7	94

[a] BMD=Bone Mineral Density; NPV=Negative Predictive Value; PPV=Positive Predictive Value

DISCUSSION

The aim of the current study was to investigate the ability of both Garvan and FRAX® to select women who sustained a subsequent fracture within two years after a recent low-energy fracture. At a group level, Garvan but not FRAX® provided a significantly higher fracture risk calculation in women who sustained a subsequent fracture compared to those who did not. However, it was not possible to predict a subsequent fracture within two years on an individual basis with either model.

According to Garvan, the five- and 10-year risk scores for any fracture in the current study were 20% and 36% respectively, the 10-year risk for a major osteoporotic fracture with FRAX® was 12%. The rates of all and major subsequent fractures were 13% and 6% during two-year follow-up, and therefore approximately half of the predicted rates over five years by Garvan and 10 years by FRAX®. This may be explained by the time-dependent subsequent fracture rate shortly after the initial fracture as reported by van Geel *et al.* in a large group of postmenopausal women[14]. They demonstrated that one out of four subsequent fractures occurred within the first year after the initial fracture. Another study showed comparable results and found that fracture rate following an osteoporotic fracture was substantially increased immediately after the initial fracture[16].

Silman proposed three possible explanations for the increased risk on subsequent fracture shortly following prior fracture[29]. First, risk factors provoking the first fracture might be still present increasing the risk of a subsequent fracture. Second, the occurrence of fractures often results in immobilisation which provokes further bone loss. Third, mechanical influences caused by the initial fracture may result in difficulties in balance with an increased risk of falls and hence subsequent fracture. Up to 70% of low-energy fractures are caused by a fall[30,31]. The timing of a subsequent fracture fluctuates over time[14]. Both Garvan and FRAX® are not taking into account this aspect in their calculations of fracture risk. Based on these results, it might be worth considering to implement timing of subsequent fracture after initial fracture in these models.

When comparing the 10-year fracture risk calculations of Garvan and FRAX® in our study population, Garvan provides a 10-year risk that is 24% higher compared to FRAX® (36% versus 12% respectively). This can be explained by the fact that Garvan provides a risk estimation for all types of fracture, while FRAX® provides a risk estimation for major osteoporotic fractures. Additionally, fall-related risk factors are excluded from the FRAX® calculations, while Garvan takes into account the number of falls in the previous 12 months. This results in an increase of fracture risk with the number of falls while fracture risk in FRAX® remains constant, regardless of the presence of a history of falls in the past 12 months[32,33]. In the current study, 17% of the women with a subsequent fracture sustained at least three falls 12 months prior to inclusion, compared to 4% of the women without a subsequent fracture. Furthermore, Garvan takes into account the number of previous fractures after 50 years of age, while FRAX® only takes into account the presence of a fracture after 50 years of age. This results in an increase of fracture risk with a higher number of multiple previous fractures according to Garvan, while FRAX® remains constant with the presence of one or more previous fractures[32,33]. In the current study, 29% of the women had a history of two or more fractures after 50 years of age.

Garvan appears to be useful for subsequent fracture risk prediction within two years after the initial fracture at a group level in the present study. However, at an individual level, both Garvan and FRAX® failed in selecting women who actually sustained a subsequent (major osteoporotic) fracture within two years. The area under the ROC curve for FRAX® showed that FRAX® calculations were not much different from random allocation, which would be equivalent to an area under the curve of 0.5. With respect to Garvan, the model showed to be better than random allocation, but it was not possible to determine an optimal cut-off value in order to select women at high risk for short term subsequent fracture. However, the negative predictive value of both instruments was high, indicating that a low fracture risk score can have a reassuring function towards patients with a low fracture risk in clinical practice.

This study has several limitations. First, we used a small and selected study population and only a small number of subsequent fractures, especially major osteoporotic fractures, occurred during follow-up. Second, the follow-up period of two years in the current study was much shorter than the Garvan (five- and 10-year) and FRAX® (10-year) model predictions. It is therefore not possible to exactly compare the percentage of subsequent fractures in the present study with the percentages as predicted by Garvan and FRAX®. Third, the models are developed for fracture risk prediction in untreated patients, while at least a part of our patients was treated with anti-osteoporosis medication during follow-up. Additionally, both Garvan and FRAX® models were not developed for patients with a recent fracture.

In conclusion, the current study showed that Garvan predicted a significantly higher fracture risk in patients who sustained a subsequent fracture within two years compared to those who did not, while FRAX® showed no difference. For individual patient assessment, although Garvan showed a significant result on the ROC curve, both fracture risk calculators were found not to be suitable for prediction of short term subsequent fracture risk in women with a recent low-energy fracture.

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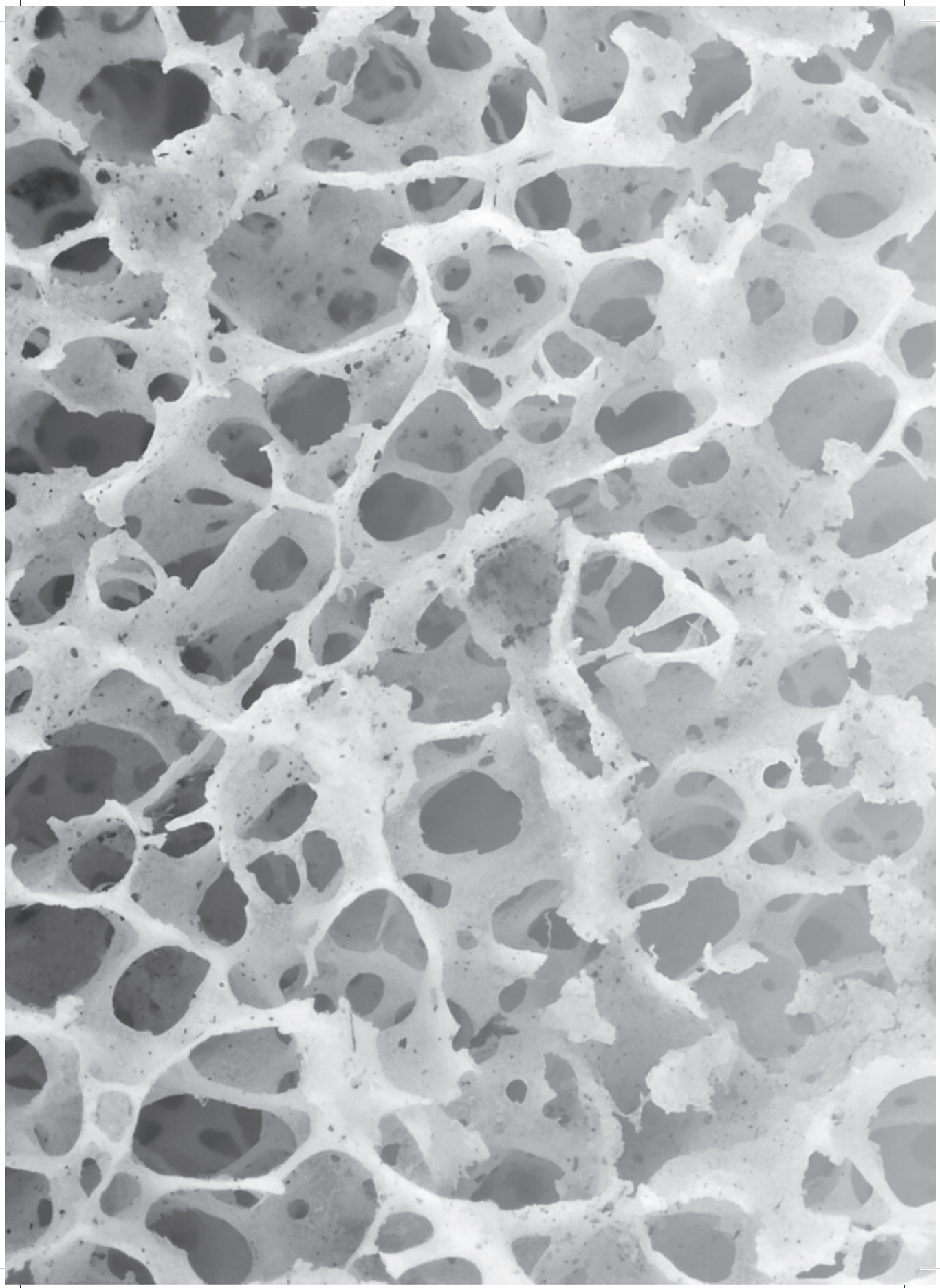

Chapter 7

General Discussion

MAIN FINDINGS

The aim of the current thesis was to assess different aspects of fracture risk in Primary care.

In chapter 2, the prevalence of previously undiagnosed vertebral fractures in women aged 50 years and older with clinical risk factors in Dutch Primary care was determined. In 31% of the women, a previously unknown vertebral fracture was found. Taking into account low bone mineral density (BMD; T-scores ≤2.5) and the presence of a vertebral fracture, 44% of the women required treatment. When T-scores alone were taken into account, only half of the women eligible for treatment would actually have been identified. Vertebral fracture assessment, added an additional 23% of the women, next to the 21% based on BMD measurement, who were eligible for treatment according to the Dutch guidelines of osteoporosis case-finding.

The measurement properties of the Activities-specific Balance Confidence (ABC16) scale, for use in a population aged 50 years and older with a recent low-energy fracture, were assessed in chapter 3. Based on the results of principle component analyses, we concluded that the structural coherence of the ABC16 comprised of one component. Internal consistency was good and confirmed that all items were measuring the same construct. A significant, but moderate, relation was found with depression, anxiety and health-related quality of life showing good construct validity of the scale in the population of interest.

In chapter 4, we investigated the occurrence of major depression (MD) in the first year after a recent low-energy fracture in women aged 50 years and older. We found that both prevalence (lifetime prevalence of 34%, 12 month period prevalence of 11%) and incidence (12 month incidence of 8%) of MD were substantially higher in women with a recent low-energy fracture compared to those reported in the general elderly population. Results showed that, of the women who became depressed during the 12 month of follow-up, 75% had suffered from a MD earlier in life. Women with a previous episode of depression had a 5.94 increased risk for another MD after a low-energy fracture. This suggests a major impact of a low-energy fracture on the occurrence of a new episode of MD, especially in women with a history of MD.

In chapter 5, the influence of depression on future falls was studied in women aged 60 years and older with a recent low-energy fracture. At baseline, 18% of the women suffered from depression according to high EDS (Edinburgh Depression Scale) scores and 44% sustained a fall during two-year follow-up. The total number of fall incidents was the same in both years, however 72% of the women sustained their first fall during the first year and 28% during the second year, meaning that the women who sustained a fall during the second year, were frequent fallers. Depression contributed the most, after adjustment for the presence of clinical risk factors, to the risk of falling over a two year period.

In chapter 6, the applicability of the Garvan nomogram and the FRAX®, both fracture risk calculators, on short term fracture risk were prospectively assessed in women aged 60 years and older with a recent low-energy fracture. During a follow-up period of two years, we found that 13% of the women sustained a subsequent fracture. Compared with the five- and 10-year fracture risk predictions of Garvan (20% and 36%, respectively), the actual fracture rate in the two-year period of follow-up was relatively high. The

same was concluded with respect to FRAX® since the 10-year prediction of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) was 12%, compared to 6% actual fracture rate in our study population over a period of two-years. The Garvan model provided a significantly higher fracture risk in women who sustained a subsequent fracture compared to those who did not, while with FRAX® no differences between both groups were found. It was not possible to predict a subsequent fracture within two years on an individual basis with either model.

IMPLICATIONS FOR CLINICAL PRACTICE

During the past years, the insight has grown that assessment of fracture risk comprises more than BMD alone. It is now well recognized that also other aspects of fracture risk should be taken into account when determining risk of fractures. A prior fracture is known to be a major risk factor for subsequent fractures, implying the relevance of fracture risk assessment in those who have already suffered from a fracture. Within fractures, the presence of a vertebral fracture can be seen as a separate predictor of subsequent fracture[1,2]. Nevertheless, most patients with vertebral fractures do not present with acute signs and symptoms. Only one in three vertebral fractures is presented as clinical vertebral fracture[3]. In the Dutch guidelines on osteoporosis 2002, indication for treatment was based on BMD outcome and the presence of a vertebral fracture, but there are no guidelines on how, when, and in whom to diagnose vertebral fractures. Following the results of chapter 2 and the findings of others, we recommend that the Dutch guidelines should include vertebral fracture assessment systematically in women aged 50 years and older who are referred for DXA in Primary care.

Results of chapter 3 through 6 were obtained from a population that sustained a recent low-energy fracture and the outcomes can be implemented in general practice such as in outpatient fracture and osteoporosis clinics. With the incorporation of risk factors in fracture prevention, most clinicians focus on the presence of skeletal-related factors (*i.e.* osteoporosis, family history of hip fracture, glucocorticoid use), while both falls and psychological aspects like fear of falling and depression also have significant influence on fracture risk[4-6]. Fear of falling and depression are highly prevalent among older individuals and both have been suggested to increase the risk for fracture-causing falls. Next to clinical risk factors, fracture prevention programs should thus also focus on the presence of fear of falling and depression.

The current available fracture risk prediction tools, like Garvan and FRAX®, are not adequately useful for clinical decision making regarding treatment of individual patients. Fracture risk assessment would benefit from a combination of the risk factors from both Garvan and FRAX®. Especially the number of falls in the past 12 months seems to add significantly in fracture risk prediction. Furthermore, the timing of subsequent fracture should be taken into account, as it has been shown that subsequent fractures cluster in time after first fracture[7].

RECOMMENDATIONS FOR FURTHER RESEARCH

We recommend to systematically perform vertebral fracture assessment in women with clinical risk factors referred for BMD measurement in Primary care. This will result in a significant number of patients

who will be diagnosed with one or more vertebral fractures and therefore would qualify for treatment. In the new Dutch guideline for osteoporosis and fracture prevention, that is only available in concept at present, special attention is focussed on patients presenting with a recent fracture and in patients at high risk for vertebral fractures.

With respect to patients with a recent low-energy fracture, more attention is also needed for psychological aspects like fear of falling and depression. The ABC16 might be suitable as a screening tool for fear of falling to identify those subjects at risk for falls, and hence, subsequent fracture. Before the ABC16 is applicable in clinical practice, further research is needed to evaluate its sensitivity and specificity in identifying those at risk.

Based on the finding of high prevalence of depression after a subsequent fracture, further research is needed to confirm our findings and to evaluate the effect of treatment and prevention of depression after a recent fracture. Early intervention strategy (psycho-education, simple cognitive behavioural intervention) in those patients at risk might help to prevent depression, and thereby subsequent falls and perhaps also fractures. Moreover, depression has been shown to be a risk factor for delayed recovery after fracture.

Risk management in clinical practice is most useful when it is possible to assess individual fracture risks on which treatment decisions can be made. The Garvan nomogram seemed most suitable for subsequent fracture risk prediction in patients with a recent fracture at a group level, rather than the FRAX® model. However, both models are currently inadequate for short term fracture risk prediction on an individual level. The two models have some overlap in their clinical risk profile, and partly they use clinical risk factors that can be seen as complementary to each other. Therefore, the development of one model would be desirable. Furthermore, neither of the two models takes into account the timing of a subsequent fracture. Further research is needed to expand Garvan and FRAX® into instruments which comprises all aspects of fracture risk (*i.e.* timing of fracture, falls, and history of fracture).

STRENGTHS AND LIMITATIONS OF THE STUDIES

This thesis described the results of five original studies based on two projects, in which strengths and limitations are present. In the project aimed at studying the prevalence of vertebral fractures in Primary care, we only included women with the presence of at least one clinical risk factor as described in the Dutch guidelines of osteoporosis 2002. We did not take into account other risk factors as known from the literature or used in other case-finding strategies as for example FRAX®. A strength of this project is that it was performed in Primary care, since the only information currently available on the presence of vertebral fracture comes from studies in secondary or tertiary institutions.

With regard to the Eindhoven Subsequent Fracture and Osteoporosis Reduction-project (ESFOR-p), it needs to be mentioned that only 40% of the patients that visited the F&O clinics participated in the study. However, despite the low response rate, the ESFOR-p population accurately reflects the population of the F&O clinic. No significant differences were found between both populations with respect to mean age and DXA outcome. Furthermore, age, DXA outcome and type of fracture, of our study sample were

comparable to a previous publication on the same F&O clinic[8]. Moreover, with respect to psychological characteristics (fear of falling and depression), our population was comparable with the literature[9,10]. A strength of the ESFOR-p study was that we followed the participants for a period of two years. However, sample size was small, resulting in a small amount of subsequent fractures.

CONCLUSIONS

Guidelines on fracture prevention should focus on detection of vertebral fractures in addition to low BMD, as vertebral fractures are highly prevalent in women in Primary care. Assessment of fracture risk should comprise a broad spectrum of risk factors. By developing fracture risk calculators such as Garvan and FRAX® there is already attention for several clinical risk factors besides BMD. However, these online available fracture risk calculators should be further extended and validated. Furthermore, clinicians should not only focus on clinical risk factors, but also on psychological aspects as depression and fear of falling. More research is needed to explore the possibility to reduce subsequent falls and fractures by screening and treating patients with a fear of falling and depression.

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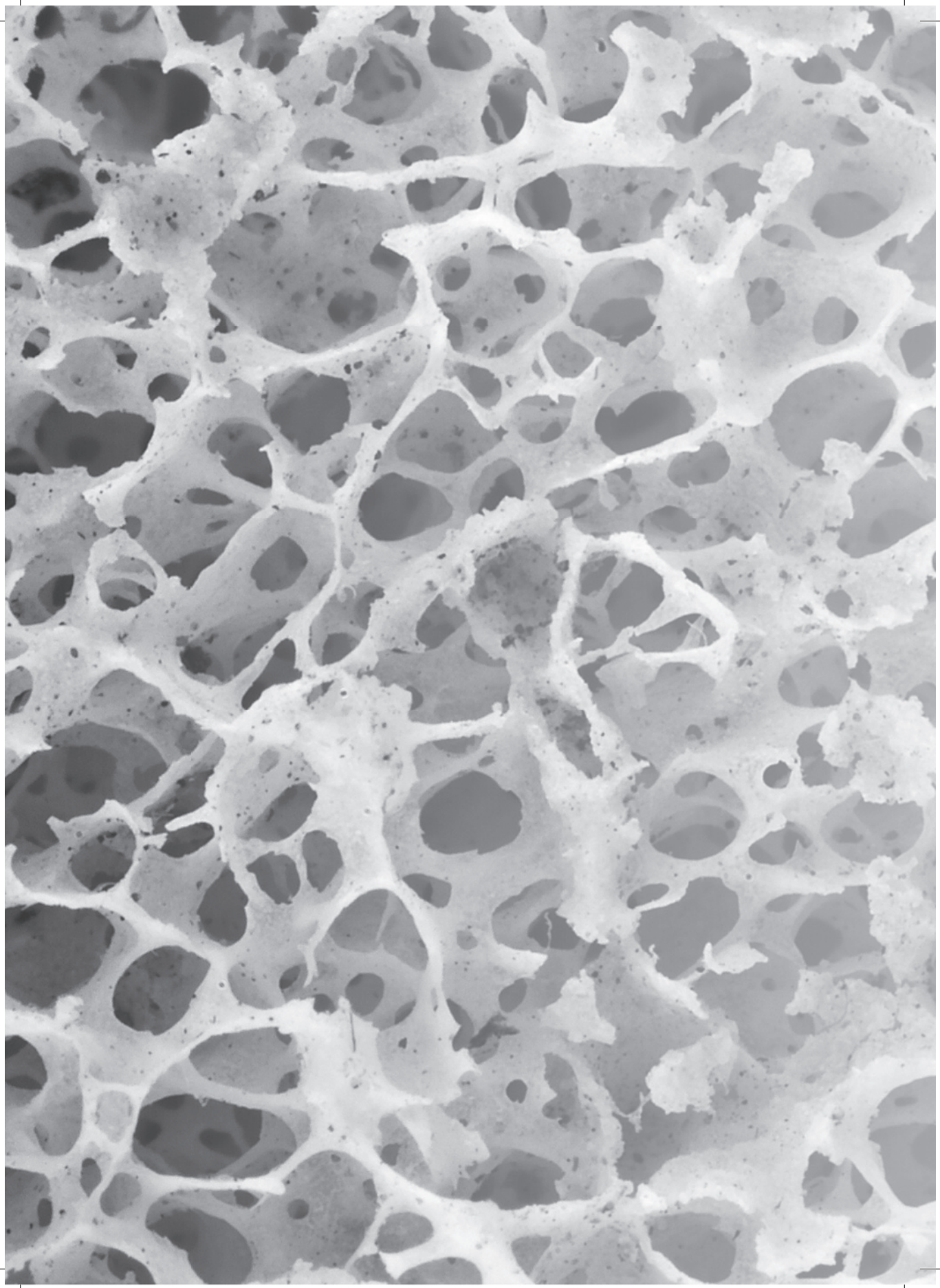


Summary

As people age, bone mass declines, which predisposes to an increased risk of fractures. The decline of bone mass and disruption of bone micro-architecture result in a systemic condition called osteoporosis. Elderly represent the fastest growing population category in the world, causing osteoporosis to be a major public health problem throughout the world. The clinical relevance of osteoporosis lies in the resulting osteoporotic fractures. Fractures are associated with increased mortality and morbidity. Moreover, economic costs are substantial. Therefore assessment of fracture risk plays a key role in osteoporosis management. The aim of this thesis was to study several aspects of fracture risk in Primary care patients.

Vertebral fractures are a known risk factor for subsequent fractures. Hence, the identification of vertebral fractures is important for decisions on fracture prevention. In chapter 2 the prevalence of previously undiagnosed vertebral fractures in women aged 50 years and older with one or more clinical risk factors in Dutch Primary care was determined. In 31% of the women, a previously unknown vertebral fracture was found. When bone mineral density (BMD) alone was taken into account, only half of the women in need for treatment would actually have been identified. Vertebral fracture assessment, added an additional 23% of the women, next to the 21% based on BMD measurement, who should be qualified for treatment according to the Dutch guidelines of osteoporosis case-finding.

Fear of falling is highly prevalent among older individuals and has been suggested to increase the risk for fracture-causing falls. It seems apparent that fracture prevention programs should thus, next to clinical risk factors, focus on the presence of fear of falling. Before implementing in clinical practice, relevant instruments to measure fear of falling need to be validated in the population of interest. In Chapter 3, the measurement properties of the Activities-specific Balance Confidence Scale (ABC-16) were examined, which was developed to assess an individual's perception of balance confidence (often used as a measure of fear of falling). In conclusion, the ABC16 was found to have good measurement properties for use in subjects with a recent low-energy fracture.

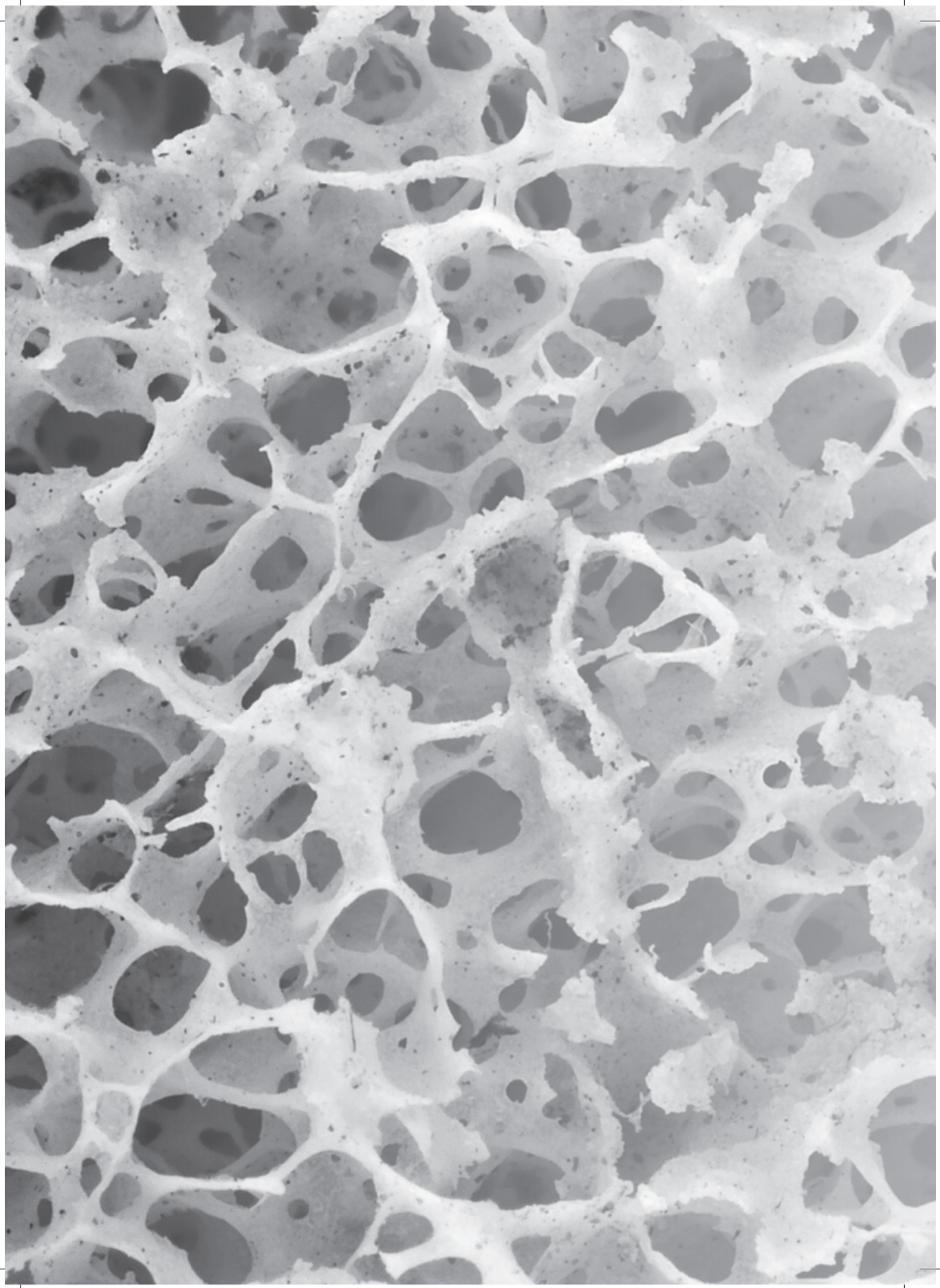
Depression has been associated with increased fracture risk and decreased BMD. Observational research regarding the occurrence of major depression (MD) after low-energy fractures is important for gaining more insight into the explanatory mechanisms of the relation between depression, fractures and BMD. In chapter 4, the prevalence and incidence of a major episode of depression during 12 months of follow-up in women aged 50 years and older who suffered from a recent low-energy fracture were described. We found that both prevalence and incidence of MD were substantially higher in women with a recent low-energy fracture compared to those reported in the general elderly population. Women with a previous episode of depression had a 5.94 increased risk for another MD after a low-energy fracture. This suggests a major impact of a low-energy fracture on the occurrence of a new episode of MD, especially in women with a history of MD.

Falls are a strong and independent risk factor for fractures in elderly people. Depression has been described as a potential risk factor for falls in various samples and settings, however its relation has not been described in women who suffered from a recent low-energy fracture. In chapter 5, the relation between depression and fall incidents in post-menopausal women with a recent low-energy fracture was studied. Depression was found to contribute the most (OR 4.14), after adjustment for the presence

of clinical risk factors, to the risk of falling over a two-year period.

A history of a fracture significantly increases the risk of subsequent fractures at other skeletal sites. The risk of a subsequent fracture is highest shortly after the initial fracture. The Garvan nomogram has been developed to assess five- and 10-year fracture risk, FRAX® calculates a 10-year fracture risk of major osteoporotic fractures (clinical spine, forearm, hip, or shoulder). In chapter 6 the applicability of both fracture risk calculators on short term fracture risk in women aged 60 years and older who had recently suffered from a low-energy fracture was studied. The Garvan model provided a significantly higher fracture risk in women who sustained a subsequent fracture compared to those who did not, while with FRAX® no differences between both groups were found. It was not possible to predict a subsequent fracture within two years on an individual basis with either model.

We concluded that guidelines on fracture prevention should focus on detection of vertebral fractures in addition to low BMD, as vertebral fractures are highly prevalent in women in Primary care. Assessment of fracture risk should comprise a broad spectrum of risk factors. By developing fracture risk calculators such as Garvan and FRAX® there is already attention for several clinical risk factors besides BMD. However, these online available fracture risk calculators should be further extended and validated. Furthermore, clinicians should not only focus on clinical risk factors, but also on psychological aspects as depression and fear of falling. More research is needed to explore the possibility to reduce subsequent falls and fractures by screening and treating patients with a fear of falling and depression.



Samenvatting

Naarmate mensen ouder worden, neemt de botmassa af, waardoor het risico op fracturen toeneemt. De afname van botmassa in combinatie met afwijkingen in de microarchitectuur van het bot resulteren in een systemische aandoening van het skelet die osteoporose wordt genoemd. Ouderen vormen de snelst groeiende bevolkingsgroep ter wereld, met als gevolg dat osteoporose een toenemend probleem zal zijn voor de volksgezondheid in de hele wereld. De klinische relevantie van osteoporose ligt in het daaruit voortvloeiende verhoogde risico op een fractuur. Fracturen zijn geassocieerd met een verhoogde morbiditeit en mortaliteit. De economische kosten daarvan zijn aanzienlijk. Om die redenen speelt de inschatting van het risico op fracturen een belangrijke rol in de behandeling van osteoporose. Het doel van dit proefschrift was om verschillende aspecten van fractuurrisico in een groep patiënten uit de eerste lijn te bestuderen.

Een belangrijke risicofactor voor een nieuwe fractuur is de aanwezigheid van een wervelfractuur. Dit impliceert dat de identificatie van wervelfracturen belangrijk is voor het nemen van beslissingen rondom fractuurpreventie. In hoofdstuk 2 wordt de prevalentie van niet eerder gediagnosticeerde wervelfracturen bij Nederlandse vrouwen van 50 jaar en ouder met één of meerdere klinische risicofactoren in de eerste lijn gemeten. Bij 31% van de vrouwen, werd met behulp van de VFA (vertebral fracture assessment) methode door middel van een laterale opname van de wervelkolom met DXA apparatuur een eerder onbekende wervelfractuur gevonden. Uit de beoordeling van de laterale scans op de aanwezigheid van wervelfracturen bleek dat, naast de 21% van de vrouwen die op basis van een botdichtheidsmeting in aanmerking kwam voor behandeling, nog eens 23% voldeed aan de behandelnormen volgens de Nederlandse richtlijnen voor osteoporose. Wanneer alleen rekening gehouden werd met botdichtheid, zou dus slechts de helft van de vrouwen die in aanmerking kwam voor behandeling daadwerkelijk worden geïdentificeerd.

Valangst komt zeer vaak voor onder oudere personen en er zijn aanwijzingen dat er een relatie bestaat tussen een verhoogde mate van valangst en een toename op fractuur gerelateerde valincidenten. Het lijkt evident dat fractuur preventieprogramma's, naast klinische risicofactoren, zich richten op de aanwezigheid van valangst. Voorafgaand aan de invoering in de klinische praktijk, is het van belang om relevante instrumenten die valangst meten te valideren in de relevante populatie. In hoofdstuk 3 werden de psychometrische eigenschappen van de Activities-specific Balance Confidence Scale (ABC-16), die werd ontwikkeld om de perceptie van het vertrouwen in het eigen evenwicht (vaak gebruikt als een maat voor valangst) te beoordelen, beschreven. De ABC16 bleek een valide instrument voor het meten van valangst voor gebruik bij patiënten met een recente laag energetische fractuur.

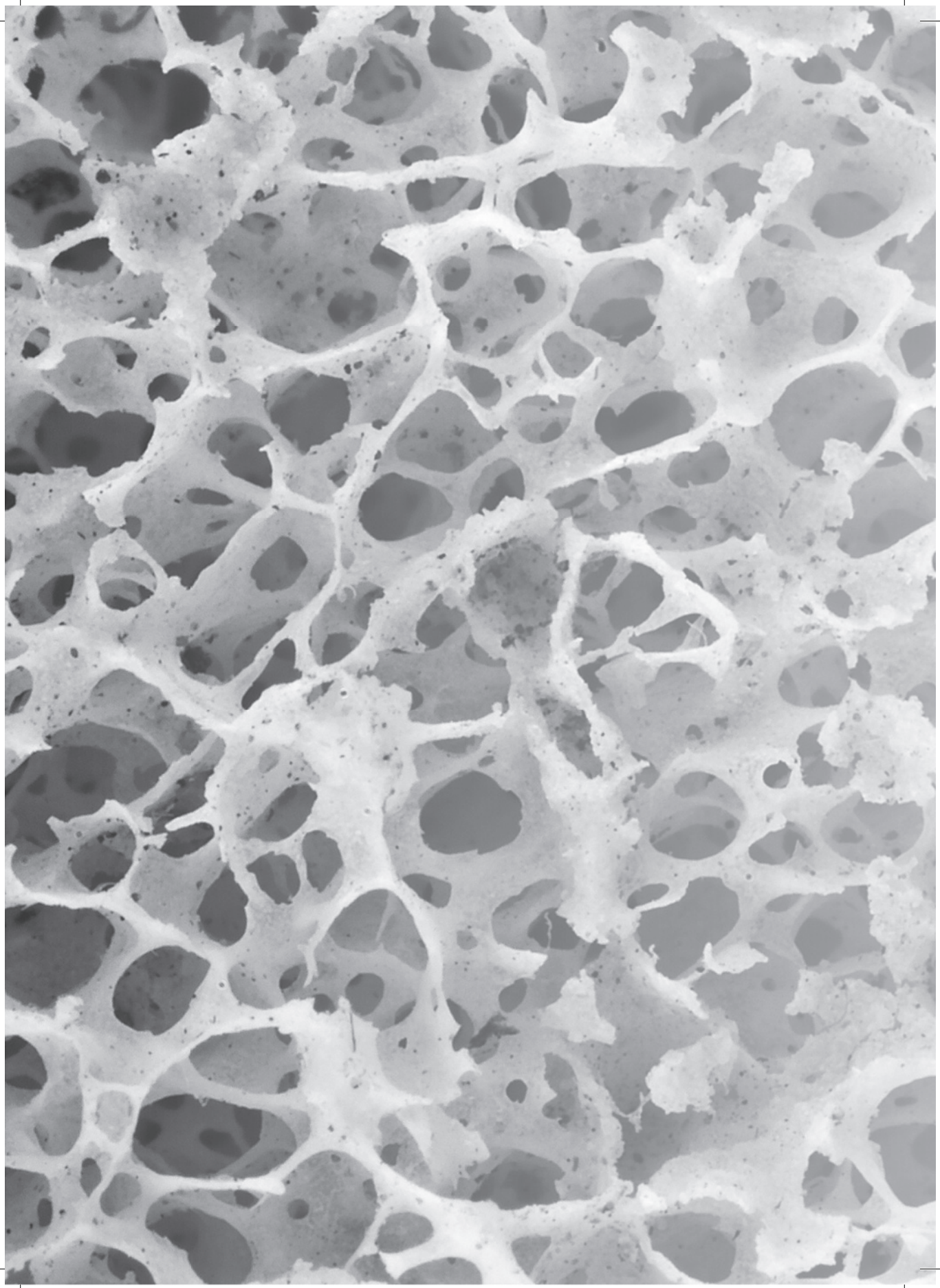
Depressie is geassocieerd met een verhoogd risico op botbreuken en verminderde botdichtheid. In de literatuur zijn diverse verklaringen gegeven vanuit verschillende invalshoeken. Observationeel onderzoek met betrekking tot het optreden van een depressie na een laag energetische fractuur is belangrijk voor het verkrijgen van meer inzicht in de verklarende mechanismen van de relatie tussen depressie, vallen, fracturen en botdichtheid. Het doel van de studie zoals beschreven in hoofdstuk 4 was om de prevalentie en incidentie van een depressie te bestuderen gedurende een periode van 12 maanden bij vrouwen van 50 jaar en ouder na een laag energetische fractuur. Zowel de prevalentie en incidentie van depressie waren aanzienlijk hoger bij vrouwen met een recente laag energetische fractuur in vergelijking met ouderen in de algemene bevolking. Bovendien hadden vrouwen met

een eerdere episode van depressie een 5,94 maal verhoogd risico voor een nieuwe episode na het doormaken van een laag energetische fractuur. Dit suggereert dat een laag energetische fractuur een grote impact heeft op de incidentie van een episode van depressie, met name bij vrouwen die een voorgeschiedenis van depressie hebben. Bovendien is gesuggereerd dat depressie het risico op een fractuur verhoogt, hetgeen betekent dat de opsporing en behandeling van depressie zou kunnen bijdragen aan het verminderen van het risico van toekomstige fracturen.

Vallen is een sterke en onafhankelijke risicofactor voor fracturen bij ouderen. Depressie is beschreven als een potentiële risicofactor voor vallen in verschillende populaties en onder verschillende omstandigheden. Deze relatie is echter nog niet onderzocht bij vrouwen die een recente laag energetische fractuur hebben doorgemaakt. Het doel van hoofdstuk 5 was om de relatie tussen depressie en valincidenten bij post-menopauzale vrouwen met een recente laag energetische fractuur te onderzoeken. Depressie bleek het meest bij te dragen (OR 4,14) aan het risico op vallen over een periode van twee jaar, na correctie voor de aanwezigheid van klinische risicofactoren.

Een eerdere fractuur verhoogt het risico op nieuwe fracturen. Het risico op een fractuur is het hoogst kort na de eerste fractuur. Het Garvan nomogram is een model ontwikkeld om het risico op fracturen over een periode van vijf- en 10-jaar te berekenen en het FRAX® model om het risico op major (klinische wervel, onderarm, heup, of schouder) fracturen over een periode van 10 jaar te berekenen. Vanwege het verhoogde risico op een nieuwe fractuur na een eerdere fractuur, is de beoordeling op fractuurrisico in de periode vlak na een fractuur van groot belang. In hoofdstuk 6 wordt het onderzoek naar de toepasbaarheid van beide fractuurrisico modellen voor het gebruik van inschatting van fractuurrisico op korte termijn bij vrouwen van 60 jaar en ouder die onlangs een laag energetische fractuur hebben doorgemaakt, beschreven. Het Garvan model voorspelde op groepsniveau een significant hoger fractuur risico bij vrouwen die daadwerkelijk een nieuwe fractuur doormaakten tijdens follow-up ten opzichte van degenen die gedurende twee jaar geen nieuwe fractuur opliepen, terwijl met FRAX® geen verschillen werden gevonden tussen beide groepen. Met betrekking tot de voorspelling van fractuurrisico op individueel niveau, concludeerden we dat geen van beide modellen een fractuur binnen twee jaar na een laag energetische fractuur kon voorspellen.

In het algemeen kunnen we uit deze studies concluderen dat de richtlijnen voor fractuur preventie zich moeten richten op de opsporing van wervelfracturen in aanvulling op opsporing van lage botdichtheid, gezien het feit dat wervelfracturen vaak voorkomen bij vrouwen in de eerste lijn zonder dat er sprake is van klachten. Bovendien zou de beoordeling van het fractuurrisico een breed spectrum van risicofactoren moeten omvatten. Door de ontwikkeling van fractuurrisico modellen, zoals Garvan en FRAX® zijn er nu mogelijkheden om verschillende klinische risicofactoren naast botdichtheid te beoordelen. Wel moeten de online beschikbare fractuurrisico calculators verder worden gevalideerd en uitgebreid alvorens deze klinisch toepasbaar zijn. Daarnaast moeten artsen zich niet alleen richten op klinisch-biologische risicofactoren, maar ook alert zijn op psychologische aspecten rondom fractuurpreventie zoals depressie en valangst. Aanvullend onderzoek is nodig naar de mogelijkheid om valincidenten en fracturen te verminderen door het screenen en behandelen van patiënten met valangst en depressie.



Dankwoord

Na vier jaar werk is het dan eindelijk zover, mijn proefschrift is af. Een proefschrift schrijf je niet alleen. Zonder de hulp en inzet van een aantal mensen was dit proefschrift er niet geweest. Ik wil dan ook iedereen bedanken die heeft bijgedragen aan het tot stand komen ervan en een aantal mensen in het bijzonder.

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Noor, Berber, Liesbeth, Sandra, Lianne, Marion, Aly, Esther, Antoinette en Corinne, dank jullie wel voor jullie steun, gezelligheid, hulp en afleiding tijdens de soms lange dagen van denken, analyseren en schrijven.

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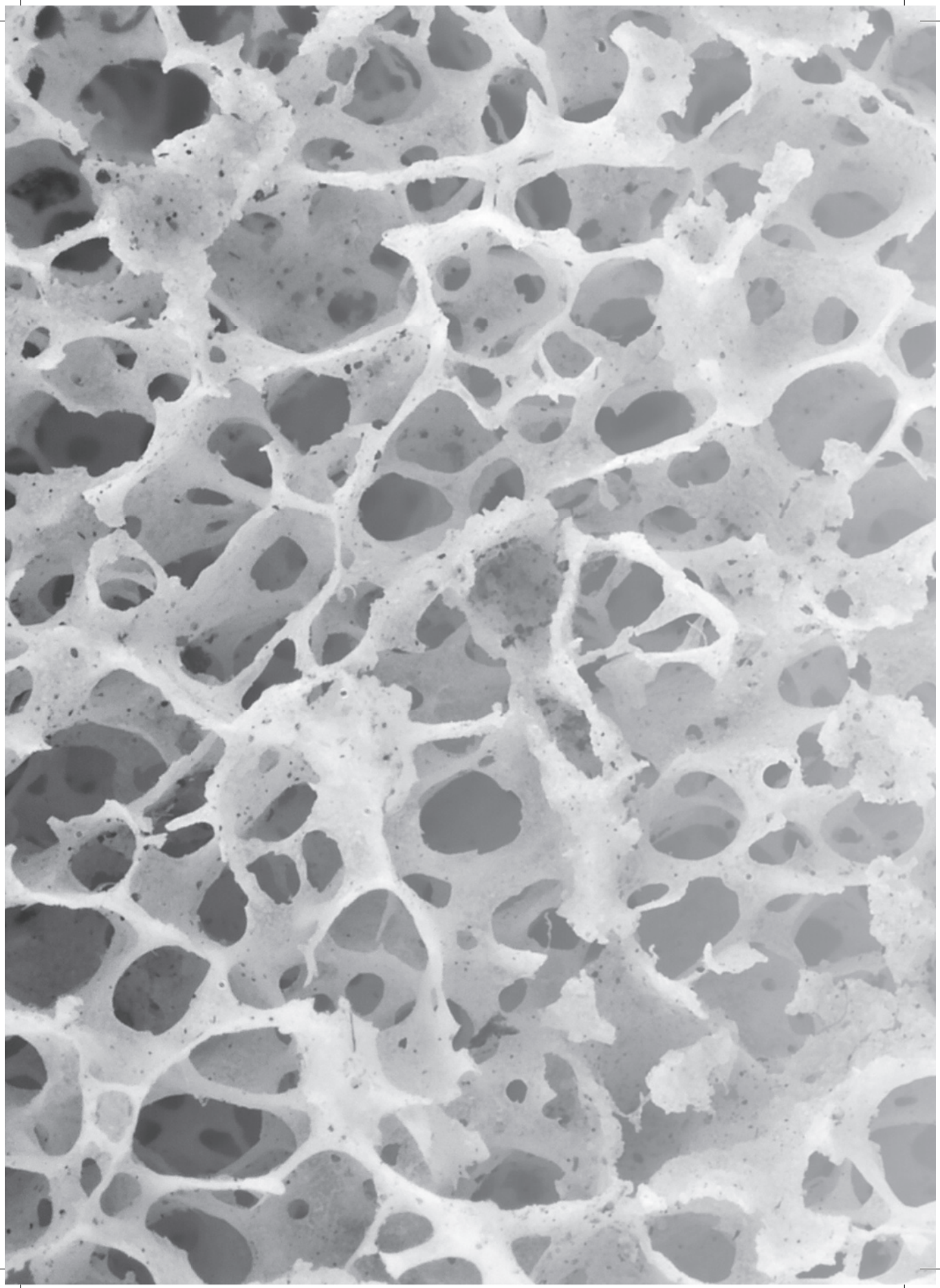
Martha, juli 2011



Curriculum Vitae

Martha van den Berg werd op 6 maart 1981 geboren in Amersfoort. Na het afronden van het Hoger Algemeen Voortgezet Onderwijs aan 't Hooghe Landt College te Amersfoort in 1998, ging zij viool studeren aan het Brabants Conservatorium te Tilburg. Aan Tilburg University begon zij in 2002 aan de opleiding psychologie. In 2007 behaalde zij haar master titel met als afstudeerrichting Psychologie en Geestelijke Gezondheid. Na haar afstuderen startte ze met haar promotieonderzoek naar fractuurrisico bij PoZoB. Daarnaast was zij de eerste twee jaar van haar promotietraject één dag in de week werkzaam als onderzoeksassistent bij een onderzoek naar Implanteerbare Cardioverter Defibrillators. Vanaf 2009 combineerde ze haar onderzoeksactiviteiten met projectmanagement rondom de ontwikkeling van de functie praktijkondersteuner GGZ bij PoZoB. In 2010 zette Martha haar onderzoeksactiviteiten voort aan Tilburg University. Na haar promotie blijft ze werkzaam als projectleider GGZ bij PoZoB.

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